L27 ANSWER 6 OF 19 CAPLUS COPYRIGHT 2003 ACS
2000:433415 Document No. 133:101470 Compositions and methods for the treatment of metabolic bone disorders and bone metastases. Chen, James (Light Sciences, Ltd., USA). PCT Int. Appl. WO 2000041725 A2 20000720, 27 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US848 20000114. PRIORITY: US 1999-PV116233 19990115.

AB The present invention is drawn to methods and compns. useful for **targeting** and treating target tissues affected by or involved in metabolic bone disorders and bone metastases with **photodynamic therapy** (PDT) in a mammalian subject. The compns. are bisphosphonates, pyrophosphates or bisphosphonate-like compds. conjugated to photosensitive agents which are optionally further conjugated to ligands which are target tissue specific **antibodies**, peptides or polymers. The methods of PDT treatment utilize these compns. to target the tissues or cells of a mammalian subject to be treated. The methods comprise irradiating at least a portion of the subject with light at a wavelength absorbed by said photosensitizing agent that under conditions of activation during **photodynamic therapy** using a relatively low fluence rate, but an overall high total fluence dose results in minimal collateral tissue damage.

L27 ANSWER 7 OF 19 MEDLINE DUPLICATE 1
2001065621 Document Number: 20530434. PubMed ID: 11076666.
Biodistribution of charged 17.1A photoimmunoconjugates in a murine model of hepatic metastasis of colorectal cancer. Hamblin M R; Del Governatore M; Rizvi I; Hasan T. (Wellman Laboratories of Photomedicine, Massachusetts General Hospital, Boston, MA 02114, USA.) BRITISH JOURNAL OF CANCER, (2000 Dec) 83 (11) 1544-51. Journal code: 0370635. ISSN: 0007-0920. Pub. country: SCOTLAND: United Kingdom. Language: English.

AB Optimizing **photodynamic therapy** involves attempting to increase both the absolute tumour content of photosensitizer and the selectivity between tumour and surrounding normal tissue. One reason why **photodynamic therapy** has not been considered suitable for treatment of metastatic tumours in the liver, is the poor selectivity of conventional photosensitizers for tumour compared to normal liver. This report details an alternative approach to increasing this selectivity by the use of **antibody**-targeted photosensitizers (or photoimmunoconjugates) to target intrahepatic tumours caused by human colorectal cancer cells in the nude mouse, and explored the role of molecular charge on the tumour-**targeting** efficiency of various fractions. The murine monoclonal **antibody** 17.1A which recognizes an antigen expressed on HT 29 cells was used to prepare tumour-specific photoimmunoconjugates with the photosensitizer chlorin e6. The conjugates had either a predominant cationic or anionic charge and were injected i.v. into tumour-bearing mice. Biodistribution 5 or 24 h later was measured by extraction of tissue samples and quantitation of chlorin e6 content by fluorescence spectroscopy. The photoimmunoconjugates were compared to the polylysine conjugates in an attempt to define the effect of molecular charge as well as **antibody targeting** [illegible] 17.1A conjugate delivered more than twice as much

photosensitizing agent or targeted prodrug product. Transcutaneous PDT is useful in the treatment of specifically selected target tissues, such as vascular endothelial tissue, the abnormal vascular walls of tumors, solid tumors of the head and neck, tumors of the gastrointestinal tract, tumors of the liver, tumors of the breast, tumors of the prostate, tumors of the lung, nonsolid tumors, malignant cells of the hematopoietic and lymphoid tissue and other lesions in the vascular system or bone marrow, and tissue or cells related to autoimmune and inflammatory disease.

L10 ANSWER 5 OF 12 BIOSEARCH COPYRIGHT 2003 ISI (R
1998:028048 The Genuine Article R) Number: 143YF. Photocytotoxic action of EGF-PVA-Sn(IV)**chlorin** e 6 and EGF-dextran-Sn(IV **chlorin** e6) internalizable conjugates on A431 cells. Gijsens A; deWitte P (Reprint). KATHOLIEKE UNIV LEUVEN, FAC FARMACEUT WETENSCHAPPEN, LAB FARMACEUT BIOL FYTOFARMACOL, VAN EVENSTR 4, B-3000 LOUVAIN, BELGIUM (Reprint); KATHOLIEKE UNIV LEUVEN, FAC FARMACEUT WETENSCHAPPEN, LAB FARMACEUT BIOL FYTOFARMACOL, B-3000 LOUVAIN, BELGIUM. INTERNATIONAL JOURNAL OF ONCOLOGY (DEC 1998 Vol. 13, No. 6, pp. 1171-1177. Publisher: INT JOURNAL ONCOLOGY, C/O PROFESSOR D A SPANDIDOS, EDITORIAL OFFICE, 1, S MERKOURI ST, ATHENS 116 35, GREECE. ISSN: 1019-6439. Pub. country: BELGIUM. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Certain tumour cells, such as squamous carcinoma cells, express an increased number of epidermal growth factor (EGF) **receptors**. The goal of this study was the targeted delivery of Sn(IV)**chlorin** e6 (SnCe6) to tumours that overexpress the EGF **receptor**. Therefore EGF was conjugated to the photosensitizer through a carrier, such as dextran (Dex) and polyvinylalcohol (PVA). These conjugates were then compared to a conjugate of the photosensitizer to dextran or PVA alone. The EGF-Dex-SnCe6 conjugates bound specifically to the EGF **receptors** of the human squamous carcinoma cell line A431 in contrast to EGF-PVA-SnCe6. However, EGF-PVA-SnCe6 exhibited a higher photocytotoxicity (IC50, 1.8 mu M) than EGF-Dex-SnCe6 (IC50, >10 mu M) and SnCe6 (IC50, >10 mu M). PVA-SnCe6 had a similar photocytotoxicity (IC50, 3.5 mu M) to EGF-PVA-SnCe6, indicating that PVA, more than EGF, plays a determinant role in the uptake of the conjugates by A431 cells. Together with the improved affinity of EGF-Dex-SnCe6 over EGF-PVA-SnCe6 for the EGF **receptor**, the former displayed a small increased photocytotoxicity over Dex-SnCe6, reflecting a limited EGF **receptor** mediated uptake effect. It was concluded that the photodynamic activity of the EGF-conjugate turns out to be strongly dependent on the carrier used.

L10 ANSWER 6 OF 12 BIOSEARCH COPYRIGHT 2003 ISI (R)
1998:145017 The Genuine Article R) Number: YW350. **Receptor**-mediated targeted drug or toxin delivery. Rihova B (Reprint). ACAD SCI CZECH REPUBL, INST MICROBIOL, VIDENSKA 1083, CS-14220 PRAGUE 4, CZECH REPUBLIC (Reprint). ADVANCED DRUG DELIVERY REVIEWS 2 FEB 1998, Vol. 29, No. 3, pp. 273-284. Publisher: ELSEVIER SCIENCE BV, PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 0169-409X. Pub. country: CZECH REPUBLIC. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The new approach to the treatment of cancer or to immunomodulation is drug **targeting**. Cellular uptake of drugs bound to a **targeting** carrier or to a targetable polymeric carrier is mostly restricted to **receptor**-mediated endocytosis. Factors that influence the efficiency of **receptor**-mediated uptake of targeted drug conjugate are the affinity of the **targeting** moieties, the [illegible] and nature of the target antigen, density of the target antigen,

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L2            15 DUP REMOVE L1  (2 DUPLICATES REMOVED)

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L2   ANSWER 1 OF 15  CAPLUS  COPYRIGHT 2003 ACS
2002:91321   Document No. 136:306070  Rapid control of wound infections by
     targeted photodynamic therapy monitored by in vivo bioluminescence
     imaging.  Hamblin, Michael R.; O'Donnell, David A.; Murthy, Naveen;
     [illegible], Christopher H.; Hasan, Tayyaba (Wellman Laboratories of
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AB The worldwide rise in antibiotic resistance necessitates the development of novel antimicrobial strategies. In this study we report on the first use of a photochem. approach to destroy bacteria infecting a wound in an animal model. Following topical application, a targeted polycationic photosensitizer conjugate between poly-L-lysine and chlorine6 penetrated the Gram (-) outer bacterial membrane, and subsequent activation with 660 nm laser light rapidly killed Escherichia coli infecting excisional wounds in mice. To facilitate real-time monitoring of infection, we used bacteria that expressed the lux operon from Photorhabdus luminescens; these cells emitted a bioluminescent signal that allowed the infection to be rapidly quantified, using a low-light imaging system. There was a light-dose dependent loss of luminescence in the wound treated with conjugate and light, not seen in untreated wounds. Treated wounds healed as well as control wounds, showing that the photodynamic treatment did not damage the host tissue. Our study points to the possible use of this methodol. in the rapid control of wounds and other localized infections.

L2 ANSWER 2 OF 15 CAPLUS COPYRIGHT 2003 ACS

2001:472002 Document No. 135:70116 Preparation of chlorin and bacteriochlorin-based aminophenyl-modified diethylenetriaminepentaacetic acid DTPA) and M2S2 conjugates for MRI contrast media and radiopharmaceuticals. Pandey, Ravindra K.; Grossman, Zachary; Kanter, Peter; Dougherty, Thomas J. (Health Research, Inc., USA). Eur. Pat. Appl. EP 1110963 A2 20010627, 28 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 2000-128019 20001220. PRIORITY: US 1999-PV171961 19991223; US 2000-739155 20001218.

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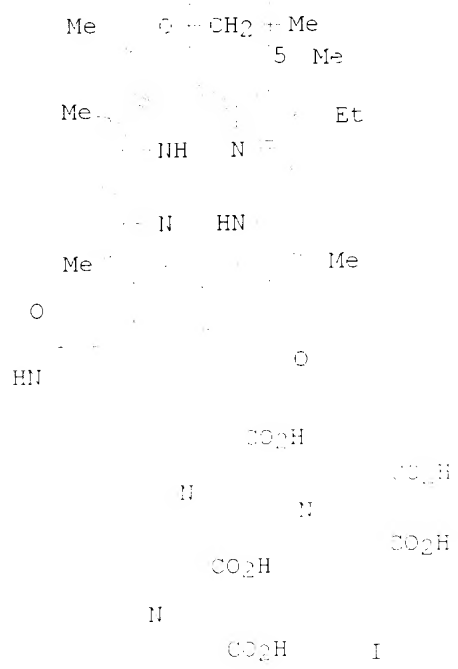

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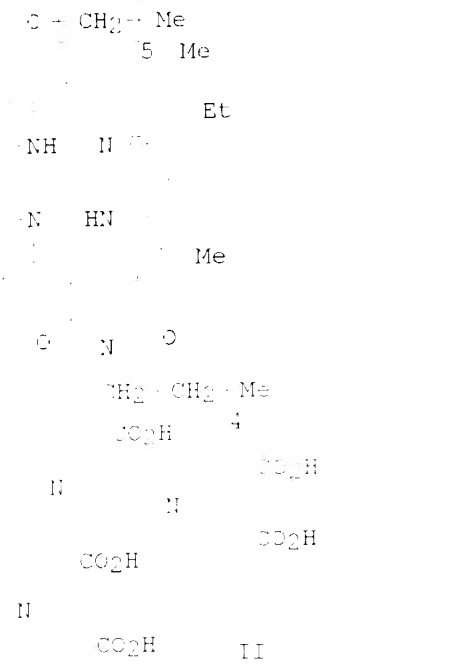

II

includes certain chlorin and bacteriochlorin-based bisaminoethanethiol (N2S2) and aminophenyl-modified diethylenetriaminepentaacetic acid (DTPA) conjugates. Example compds. include a Gd(III) chelate of HPPH-aminophenylDTPA conjugate compd. with a pheophorbide deriv., I, or a Gd-III) chelate of the purpurin-18-imide analog II, among others. When the radioactive element can form cations, the compd. is usually a chelate with the porphyrin or chlorin structure. When the element forms anions, the compd. is usually a direct chem. combination of the radioactive element into the porphyrin or chlorin structure. The invention further includes the method of using the compds. of the invention for diagnostic imaging of hyperproliferative tissue such as tumors and new blood vessel growth as is assocd. with the wet form of age-related macular degeneration. The invention further includes methods of making the compds. Compds. for MRI contrast imaging of the invention are usually Tc99, In-111 or Gd III complexes of compds. of the invention.

L2 ANSWER 3 OF 15 CAPLUS COPYRIGHT 2003 ACS
2000:51164 Document No. 132:88141 Targeted photodestruction of human colon cancer cells using charged 17.1A chlorine6 immunoconjugates. Del Governatore, M.; Hamblin, M. R.; Piccinini, E. E.; Ugolini, G.; Hasan, T. (Wellman Laboratories of Photomedicine, Department of Dermatology, Harvard Medical School, Massachusetts General Hospital, Boston, MA, 02114, USA). British Journal of Cancer, 82(1), 56-64 (English) 2000. CODEN: BJCAAI. ISSN: 0007-0920. Publisher: Churchill Livingstone.

AB The goal of this study was to develop a strategy for the selective destruction of colorectal cancer cells. Towards this end, photoimmunoconjugates were prepd. between the anti-colon cancer monoclonal antibody 17.1A and the photosensitizer (PS) chlorine6 (ce6). Polylysine linkers bearing several ce6 mols. were covalently attached in a site-specific manner to partially reduced IgG mols., which allowed photoimmunoconjugates to bear either cationic or anionic charges. The conjugates retained immunoreactivity as shown by enzyme-linked immunosorbent assays and by competition studies with native antibody. The overall charge on the photoimmunoconjugate was an important determinant of PS delivery. The cationic photoimmunoconjugate delivered 4 times more ce6 to the cells than the anionic photoimmunoconjugate, and both 17.1A conjugates showed, in comparison to non-specific rabbit IgG conjugates, selectivity for Antigen-pos. target cells. Illumination with only 1 J cm-2 of 666 nm light reduced the no. of colony forming cells by more than 99% for the cationic 17.1A conjugate and by 73% for the anionic 17.1A conjugate after incubation with 1 .mu.M ce6 equivalent of the resp. conjugates. By contrast, 1 .mu.M free ce6 gave only a 35% redn. in colonies. These data suggest photoimmunoconjugates may have applications in photoimmunotherapy where destruction of colorectal cancer cells is required.

L2 ANSWER 4 OF 15 CAPLUS COPYRIGHT 2003 ACS
1999:51641 Document No. 130:121946 Conjugate for differentiation of diseased and healthy tissue. Stolz, Hannsjoerg; Wunder, Andreas; Schrenk, Hans-Hermann; Stehle, G. (Deutsches Krebsforschungszentrum Stiftung des Oeffentlichen Rechts, Germany). Ger. Offen. DE 19741741 A1 19990128, 10 pp. German. CODEN: GWXXBX. APPLICATION: DE 1997-19741741 19970919.

AB During surgical removal of diseased tissue, the diseased tissue is differentiated from healthy tissue by use of a conjugate of a fluorescent compd. and a.gtoreq.1 carrier which becomes concd. in a specific tissue (e.g. a tumor). The carrier is e.g. a protein or polyether which is not recognized as foreign by the patient's body, and is coupled to the fluorophore by an ester, amide, or anil linkage. Suitable carriers

L2 ANSWER 5 OF 15 CAPLUS COPYRIGHT 2003 ACS
1999:21976. Document No. 131:14514 Adenoviruses synergize with nuclear localization signals to enhance nuclear delivery and photodynamic action of internalizable conjugates containing chlorin e6. Akhlynina, Tamara V.; Jans, David A.; Statsyuk, Natalia V.; Balashova, Irina Y.; Toth, Gabor; Pavo, Imre; Rosenkranz, Andrey A.; Naroditsky, Boris S.; Sobolev, Alexander S. Department of Biophysics, Biological Faculty, Moscow State University, Moscow, 119899, Russia . International Journal of Cancer, 81(5), 734-741 (English) 1999. CODEN: IJCNAW. ISSN: 0020-7136. Publisher: Wiley-Liss, Inc..

AB Photosensitizers, mols. that produce active oxygen species upon activation by visible light, are currently being used in photodynamic therapy (PDT) to treat cancer and other conditions, where limitations include normal cell and tissue damage and assocd. side effects, and the fact that cytotoxic effects are largely restricted to the plasma and other peripheral membranes. In this study, we used insulin-contg. conjugates to which variants of the simian-virus-SV40 large-tumor antigen (T-ag) nuclear localization signal (NLS) were linked in order to target the photosensitizer chlorin e6 to the nucleus. NLSs were included either as peptides coupled covalently to the carrier bovine serum albumin, or within the coding sequence of .beta.-galactosidase fusion proteins. The most potent photosensitizing conjugate was the NLS-contg. T-ag .beta.-galactosidase fusion protein (P10)-(chlorin e6)-insulin, exhibiting an ED50 more than 2400-fold lower than the value for free chlorin e6, and more than 15-fold lower than that of an NLS-deficient .beta.-galactosidase-(chlorin e6)-insulin construct, thus demonstrating that NLSs can increase the photosensitizing activity of chlorin e6. Attenuated adenoviruses were used to increase the nuclear delivery of conjugates through its endosomal-membrane-disrupting activity. In the case of the NLS-contg. P10-conjugate, co-incubation with adenovirus increased the proportion of cells whose nuclear photosensitizing activity was higher than that in the cytoplasm by 2.5-fold. This use of adenoviruses in conjunction with photosensitizers has clear implications for achieving efficient cell-type-specific PDT.

L2 ANSWER 6 OF 15 CAPLUS COPYRIGHT 2003 ACS
1999:458149 Document No. 131:148533 In vivo fluorescence imaging of the transport of charged chlorin e6 conjugates in a rat orthotopic prostate tumour. Hamblin, M. R.; Rajadhyaksha, M.; Momma, T.; Soukos, N. S.; Hasan, T. (Wellman Laboratories of Photomedicine, WEL 224, Harvard Medical School, Massachusetts General Hospital, Boston, MA, 02114, USA). British Journal of Cancer, 81(1), 261-268 (English) 1999. CODEN: BJCAAI. ISSN: 0007-0920. Publisher: Churchill Livingstone.

AB Polymeric drug conjugates are used in cancer therapy and, varying their mol. size and charge, will affect their in vivo transport and extravasation in tumors. Partitioning between tumor vasculature and tumor tissue will be of particular significance in the case of photosensitizer conjugates used in photodynamic therapy, where this partitioning can lead to different therapeutic effects. Poly-L-lysine chlorin e6 conjugates derived from polymers of av. Mr 5000 and 25 000 were prepd. both in a cationic state and by poly-succinylation in an anionic state. A fluorescence scanning laser microscope was used to follow the pharmacokinetics of these conjugates in vivo in an orthotopic rat prostate cancer model obtained with MatLyLu cells. Fluorescence was excited with the 454-528 nm group of lines of an argon laser and a 570 nm long pass filter used to isolate the emission. Results showed that the conjugates initially bound to the walls of the vasculature, before extravasating into

with differences in aggregation state between conjugates.

L2 ANSWER 7 OF 15 CAPLUS COPYRIGHT 2003 ACS
1999:423300 Document No. 131:269033 Cooperativity between free and N-(2-hydroxypropyl) methacrylamide copolymer bound adriamycin and meso-chlorin e6 monoethylene diamine induced photodynamic therapy in human epithelial ovarian carcinoma in vitro. Li, Jing Ming; Peterson, C. Matthew; Gue-Shiah, Jane; Su, Zhong-Wei; Peterson, C. Anthony; Straight, Richard C.; Kopecek, Jindrich (Division of Reproductive Endocrinology and Infertility, Department of Obstetrics and Gynecology, University of Utah School of Medicine, Salt Lake City, UT, 84132, USA). International Journal of Oncology, 15(1), 5-16 English. 1999. CODEN: IJONES. ISSN: 1019-6439. Publisher: International Journal of Oncology.
AB The purpose of this study was to det. the interaction between free unbound and N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer bound adriamycin and meso-chlorin e6 monoethylene diamine (Mce6) induced photodynamic therapy in combination in their cytotoxic activities against human ovarian epithelial carcinoma (OVCAR-3) in vitro. The effects of each agent (free drugs and HPMA copolymer bound) alone and in combination were measured simultaneously utilizing two measures of cell viability: a) mitochondrial respiration via the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide redn. (MTT) assay; and b) thymidine incorporation via the tritiated thymidine incorporation (TI) assay. These were performed at 72 and 144 h after drug exposure. Forty-eight hours from time zero (4 h after drug addn.), the cells treated with Mce6 (free and HPMA copolymer bound) and controls were exposed to 650 nm light (13 min at 15 mW/cm2, 11.7 J/cm2). The calcd. ED50 values by the MTT 72 h assay for adriamycin (A) and Mce6/light (C) were 1.5 .mu.g/mL and 209 ng/mL, resp. Adriamycin demonstrated progressive cellular toxicity over time in both assays. Mce6/light demonstrated initial damage at 72 h by MTT and TI which recovered by 144 h. Adriamycin and Mce6/light acted cooperatively to increase the percentage of cells inhibited. In combination, 21.2+-1.5% MTT redn. activity was obsd. by free adriamycin and Mce6/light compared to the expected 27.+-.5% ($p<0.0001$) based on additivity. Twice the ED50 of adriamycin (2A) (3 .mu.g/mL) or Mce6/light (2C=418 ng/mL) resulted in only 41.+-.3.6% and 39.2+-2.6% activity, resp. (both $p<0.0001$ vs. combination). When Mce6/light at 10x ED50 (10C) was combined with 1x ED50 of adriamycin (1A), or the reciprocal combination, addnl. cooperativity was demonstrated. Compared to free drugs, both HPMA copolymer bound adriamycin (P-A) and HPMA copolymer bound Mce6/light (P-C) required a 10-fold increase in drug concn. to show equivalency with free drugs (A or C). Dose response curves demonstrated a reduced slope compared to free drugs in the same dose ranges. When P-A was added (1-10x free adriamycin ED50) to an effective concn. of P-C (10P-C: equiv. to 10x free Mce6 ED50) an improved long-term inhibition of OVCAR-3 cell multiplication was noted in both the MTT and TI 144 h assays. P-C (1-10x free Mce6 ED50) added to an effective concn. of P-A (10P-A: equiv. to 10x free adriamycin ED50) did not appear to significantly improve the efficacy profile of P-A. A and C in vitro appear to act independently and are cooperative in their combined toxicity against the human ovarian epithelial carcinoma cell line OVCAR-3. HPMA polymer-adriamycin and Mce6 conjugates (P-A and P-C, resp.) inhibited growth of OVCAR-3 in vitro. HPMA copolymer-adriamycin added to HPMA copolymer-Mce6 improved the efficacy of HPMA copolymer-Mce6.

L2 ANSWER 8 OF 15 CAPLUS COPYRIGHT 2003 ACS
1999:92027 Document No. 130:193715 Photocytotoxic action of EGF-PVA-Sn(IV)chlorin e6 and EGF-dextran-Sn(IV)chlorin e6 internalizable

CODEN: IJONES. ISSN: 1019-6439. Publisher: International Journal of Oncology.

AB Certain tumor cells, such as squamous carcinoma cells, express an increased no. of epidermal growth factor (EGF) receptors. The goal of this study was the targeted delivery of Sn(IV)chlorin e6 (SnCe6) to tumors that overexpress the EGF receptor. Therefore EGF was conjugated to the photosensitizer through a carrier, such as dextran (Dex) and polyvinyl alc. (PVA). These conjugates were then compared to a conjugate of the photosensitizer to dextran or PVA alone. The EGF-Dex-SnCe6 conjugates bound specifically to the EGF receptors of the human squamous carcinoma cell line A431 in contrast to EGF-PVA-SnCe6. However, EGF-PVA-SnCe6 exhibited a higher photocytotoxicity (IC50, 1.8 .mu.M) than EGF-Dex-SnCe6 (IC50, 10 .mu.M) and SnCe6 (IC50), 5.0 .mu.M). PVA-SnCe6 had a similar photocytotoxicity (IC50), 3.5 .mu.M) to EGF-PVA-SnCe6, indicating that PVA, more than EGF, plays a determinant role in the uptake of the conjugates by A431 cells. Together with the improved affinity of EGF-Dex-SnCe6 over EGF-PVA-SnCe6 for the EGF receptor, the former displayed a small increased photocytotoxicity over Dex-SnCe6, reflecting a limited EGF receptor mediated uptake effect. It was concluded that the photodynamic activity of the EGF-conjugate turns out to be strongly dependent on the carrier used.

L2 ANSWER 9 OF 15 CAPLUS COPYRIGHT 2003 ACS

1997:640575 Document No. 127:304908 Photodynamic therapy using nuclear hormone receptors to target photosensitizers. Mohr, Scott C.; Ray, Rahul (Trustees of Boston University, USA; Mohr, Scott C.; Ray, Rahul). PCT Int. Appl. WO 9734667 A2 19970925, 56 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1997-US4542 19970321. PRIORITY: US 1996-13671 19960322.

AB The invention exploits a novel mechanism for photosensitizer localization, namely interaction with the high-affinity receptors which mediate the hormonal signals transmitted by steroids (and some other hormones such as thyroxine, retinoids, and members of vitamin D family). These receptors are expressed only in specific cell types - and by their expression they confer hormone sensitivity on these cells. The invention provides hormone/chromophore conjugates which have reasonable binding affinity towards the hormone receptor protein and methods of administering them to patients as specific photosensitizing agents which can direct lethal damage towards receptor-pos. cell lines upon irradn. with visible light. These hormone-chromophore conjugates bound to nuclear hormone receptors can be used as selective mol. delivery systems for photodynamic therapy.

L2 ANSWER 10 OF 15 CAPLUS COPYRIGHT 2003 ACS

1997:[illegible] Document No. 127:[illegible] Solution and Photoproperties of N-(2-Hydroxypropyl)methacrylamide Copolymer-Meso-chlorin e6 Conjugates. Vinsh, Jane A.C; Konak, Destmir; Spikes, John D.; Kopecek, Jindrich (Departments of Pharmaceutics and Pharmaceutical Chemistry/CCCD and of Bioengineering, University of Utah, Salt Lake City, UT, 84112, USA). Journal of Physical Chemistry B, 101 [illegible], 6803-6809 (English) 1997. CODEN: JPCBFK. ISSN: 1089-5647. Publisher: American Chemical Society.

AB The soln. properties of N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers contg. various nos. of meso-chlorin e6 monoethylenediamine

the various derivs. were also examd. Reactions were measured in aq. sodium phosphate buffer (SPB) and EtOH. The dynamic light scattering data indicate that the intermol. aggregation of Mce6 species within the HPMA copolymer conjugates is not important at the conjugate concn. measured (5 .times. 10-4 g/mL). However, intramol. aggregation of the hydrophobic Mce6 moieties does occur and was studied using absorption and fluorescence techniques. The degree of intramol. aggregation was decreased by the addn. of detergents or EtOH to the SPB solns. The cationic detergent, CTAB, strongly enhanced the fluorescence of the copolymer conjugates due to its efficient electrostatic interactions with the negatively charged Mce6 species. It also significantly increased the relative quantum yield of O uptake during the copolymer conjugate-sensitized photooxidn. of furfuryl alc. The obsd. iodide quenching of copolymer conjugate fluorescence implies that hydrophobic domains of aggregated Mce6 moieties may exist in SPB solns. of the conjugates. The time-resolved fluorescence decay measurements showed that about 15% of the Mce6 species are aggregated in SPB solns. of those copolymer conjugates with the highest Mce6 content. There was no aggregation of free Mce6 mols. in SPB solns. at the concns. used.

L2 ANSWER 11 OF 15 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
96327196 EMBASE Document No.: 1996327196. Chlorin-oligonucleotide conjugates: Synthesis, properties, and red light-induced photochemical sequence-specific DNA cleavage in duplexes and triplexes. Boutorine A.S.; Brault D.; Takasugi M.; Delgado O.; Helene C.. Laboratoire de Biophysique, INSERM U201, CNRS URA 481, 43 Rue Cuvier,75231 Paris Cedex 05, France. Journal of the American Chemical Society 118,40 (9469-9476) 1996. ISSN: 0002-7863. CODEN: JACSAT. Pub. Country: United States. Language: English. Summary Language: English.

AB Conjugates of oligonucleotides with chlorin-type photosensitizers were prepared. Two chlorin moieties, CPP and CHEVP, characterized by a modified pyrrole unit bearing an aldehyde chain, were photochemically prepared from protoporphyrin and heptaethylvinylporphyrin, respectively. These chlorin moieties were coupled through the carboxylic acid side-chain (CPP) or aldehyde side-chain (CHEVP) to the 3'-activated phosphate of oligodeoxynucleotides. Diamine or dihydrazide were used as linkers. The resulting conjugates were purified by HPLC and characterized by electrophoresis, UV-visible spectroscopy, and mass spectrometry. The photosensitizing properties of the conjugate of CHEVP with the 14-mer oligodeoxynucleotide TTCTTCTTCTTTCT were investigated using three different targets. A single-stranded 28-mer containing the complementary sequence of the 14-mer formed a double helix with the chlorin-14-mer conjugate. A 24 base-pair duplex and a 41-mer hairpin with 18 base pairs and a five nucleotide loop formed triple helices with the conjugate. In all cases, upon irradiation with visible light (428 or 668 nm), piperidine-labile sites at guanine positions were produced. The reaction required oxygen and was inhibited to some extent by sodium azide. The cleavage sites were correlated with the chlorin position in both the duplex and triplex structures. In the 41-mer hairpin, the most reactive guanines were those located in the loop region. The quantum yield for cleavage of the hairpin structure was determined to be about 10-3, independent of the excitation wavelength. This modest value is largely compensated by the high absorption of the chlorin in the red, making the conjugate highly efficient even under low light fluence. No effect was found with a noncomplementary chlorin-oligonucleotide conjugate. These results show that site-directed damages to nucleic acid structures can be achieved using oligonucleotide-**chlorin conjugates** and red light irradiation.

Louis J.; Meyer, Damon L.; Mallett, Robert W.; Kasina, Sudhakar; Reno, John M.; Axworthy, Donald B.; Gustavson, Linda M. (Neorx Corp., USA). PCT Int. Appl. WO 9515979 A1 19950615, 251 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US14174 19941207. PRIORITY: US 1993-162418 19931207.

AB Methods, compds., compns. and kits that relate to pretargeted delivery of diagnostic and therapeutic agents are disclosed. Examples include e.g. in vivo anal. of a radiolabeled chelate biotin conjugate administered after antibody pretargeting, clearing agent evaluation, two- and three-step pretargeting methodol., and prepn. of conjugates. The methodol. may also be used to increase photosensitizing agent localization.

L2 ANSWER 13 OF 15 CAPLUS COPYRIGHT 2003 ACS

1993:641670 Document No. 119:241670 Polymer conjugates for the simultaneous delivery of neoplasm inhibitor activatable by enzymes and light.. Kopecek, Jindrich; Krinick, Nancy (University of Utah, USA). PCT Int. Appl. WO 9314142 A1 19930722, 69 pp. DESIGNATED STATES: RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1993-US613 19930121. PRIORITY: US 1992-824924 19920121.

AB Neoplasm inhibitors comprise a copolymeric carrier having attached thereto both an anticancer drug and a photoactivatable drug, and/or a mixt. of copolymeric carriers wherein one copolymeric carrier has attached an anticancer drug and the other copolymeric carrier has attached a photoactivatable drug. The anticancer drug is attached to the polymeric carrier by side chains which are stable in the blood stream but susceptible to hydrolysis by lysosomal enzymes intracellularly. The photoactivatable drug is attached by either the same degradable side chain or by a nondegradable attachment. The polymer carrier may optionally contain a targeting moiety. Upon administration, polymeric macromols. enter targeted cancer cells by pinocytosis which reduces the side effects normally elicited by the free drugs. A time lag is allowed following administration for optimal uptake of the copolymers in the cancerous tissue for the anticancer agent to begin to take effect. Then a light source of the appropriate wavelength and energy is applied to activate the photoactivatable drug. The combined effect of the anticancer agent and photoactivable drug provides greater cell destruction at reduced dosages and side effects. MA-Gly-Phe-Leu-Gly-ONp (MA = methacryloyl; Np = p-nitrophenyl) was copolymd. with N-(2-hydroxypropyl)methacrylamide and adriamycin was attached to the peptide side chain. A similar copolymer comprising mesochlorin e6 attached to a glycine side chain was also prepd. The 2 copolymers were administered simultaneously to mice bearing C1300 neuroblastoma tumors followed two days later by laser irradn. The treatment resulted in sharp decrease of the tumor vol.

L2 ANSWER 14 OF 15 CAPLUS COPYRIGHT 2003 ACS

1991:674766 Document No. 115:274766 Hematopoietic cell destruction by photoactivatable compounds conjugated to amino acids and saccharides. Carlson, Dennis A. (MARTOR, USA). U.S. US 5024764 A 19910618, 7 pp. (English). CODEN: USXXAM. APPLICATION: US 1989-340453 19890227.

AB A method for the destruction of hematopoietic cells capable of attaching host cells in vivo, to prevent cellular attack of endogenous cells, comprises contacting cells with a cytotoxic agent contg. a cell-directing ligand specific for binding to the hematopoietic cells, a linking moiety, and a photoactivatable toxic component; and irradiating these cells with light at appropriate wavelength to kill the hematopoietic cells. The method and compns. are particularly useful in organ transplant and

after the injection, the animals were anesthetized and the immobilized limbs were selectively exposed to 630-670 nm light to yield a total dosage of .apprx.50 J/cm. Animals that received the phototoxic therapy showed accelerated redn. of joint swelling and inflammation as compared to the controls who received either light exposure or treatment with I alone.

L2 ANSWER 15 OF 15 MEDLINE COPYRIGHT 2003 ISI (R)
90:506083 The Genuine Article (R) Number: DY309. PHOTODYNAMIC-ACTION OF CONCANAVALIN-A-**CHLORIN CONJUGATE**-E6 ON HUMAN FIBROBLASTS. AKHLYNINA T V (Reprint); GULAK P V; SEREBRYAKOVA N V; ROZENFANTS A A; SOBOLEV A S. MINIST PUBL HLTH USSR, INST APPL MOLEC BIOL, BIOMEMBRANES LAB, MOSCOW, USSR (Reprint). BULLETIN OF EXPERIMENTAL BIOLOGY AND MEDICINE (1990) Vol. 109, No. 2, pp. 183-184. Pub. country: USSR. Language: ENGLISH.

=> s chlorin
L3 6614 CHLORIN

=> s l3 and VEGF receptor antibody
L4 0 L3 AND VEGF RECEPTOR ANTIBODY

=> s l3 and antibody
L5 238 L3 AND ANTIBODY

=> s l5 and targeting
L6 57 L5 AND TARGETING

=> s l6 and neovasculature
L7 1 L6 AND NEOVASCULATURE

=> d l7 cbib abs

L7 ANSWER 1 OF 1 CAPLUS COPYRIGHT 2003 ACS
2001:597738 Document No. 135:149265 Methods and compositions for treating condition of the eye. Miller, Joan W.; Gragoudas, Evangelos S.; Kenna, Reem S. (Massachusetts Eye and Ear Infirmary, USA). PCT Int. Appl. WO 2001058240 A1 20010816, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US4231 20010209. PRIORITY: US 2000-PV181641 20000210.

AB Provided are methods and compns. for the photodynamic therapy (PDT) of ocular conditions characterized by the presence of unwanted choroidal **neovasculature**, for example, neovascular age-related macular degeneration. The selectivity and sensitivity of the PDT method can be enhanced by combining the PDT with an anti-angiogenesis factor, for example, angiostatin or endostatin, or with an apoptosis-modulating factor. Furthermore, the selectivity and sensitivity of the PDT may be further enhanced by coupling a **targeting** moiety to the photosensitizer so as to target the photosensitizer to choroidal **neovasculature**.

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PROCESSING COMPLETED FOR L8
L10             1 DUP REMOVE L8 (5 DUPLICATES REMOVED)

=> d l10 1-12 abib abs

L10  ANSWER 1 OF 12  CAPLUS  COPYRIGHT 2003 ACS
2002:464122  Document No. 138:214139  Photoimmunotherapies for cancer using
     photosensitizer immunoconjugates and combination therapies.  Hasan,
     Tayyaba; Savellano, Mark D.; Skobe, Mihaela (The General Hospital
     Corporation, USA).  PCT Int. Appl. WO 2002100326 A2 20021219, 123 pp.
     DESIGNATED STATES: W:  AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ,
     CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE,
     GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
     LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO,
     RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN,
     YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF,
     CG, CH, CI, CM, GA, GN, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML,
     MR, NE, NL, PT, SE, SN, TD, TG, TR.  (English).  CODEN: PIXXD2.
     APPLICATION: WO 2002-US18776 20020501.  PRIORITY: US 2001-PV287767
     20010501; US 2001-PV338961 20011207.
AB   The present invention relates to photosensitizer immunoconjugate compns.
     and combination therapies for use in cancer related photodynamic
     treatments and diagnostic methods.  Photosensitizer immunoconjugates
     comprising a photosensitizer conjugated to a tumor-specific and/or
     tumoricidal **antibody** and processes for the prepn. thereof are
     described.  The use of photosensitizer immunoconjugates (PICs) offers
     improved photosensitizer delivery specificity for diagnostic and
     therapeutic applications.  In examples provided, prepn. of PEGylated
     verteporfin (BPD-MA)-**antibody** conjugates is described and
     results on its cellular uptake, subcellular localization, photochem.
     properties and cytotoxic photodynamic action presented.  The antitumor
     activity of the immunoconjugate is enhanced by combination therapy with
     tumoricidal **antibodies** such as C225.  Specificity of the
     verteporfin-C225 conjugate towards EGFR-pos. cells is also shown.

L10  ANSWER 2 OF 12  CAPLUS  COPYRIGHT 2003 ACS
2002:521462  Document No. 137:88442  Incensole and furanogermacrens and
     compounds in treatment for inhibiting neoplastic lesions and
     microorganisms.  Shanahan-Prendergast, Elisabeth (Ire.).  PCT Int. Appl. WO
     2002053138 A2 20020711, 68 pp.  DESIGNATED STATES: W:  AE, AG, AT, AU, BB,
     BG, CA, CH, CN, CO, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE,
     GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS,
     LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO,
     RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN,
     YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW:  AT, BE, CH, CY, DE, DK,
     ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI,
     CM, GA, GN, GW, ML, MR, NE, SN, TD, TG.  (English).
     CODEN: PIXXD2.  APPLICATION: WO 2002-IE1 20020110.  PRIORITY: IE 2001-2
     01 103.
AB   The invention discloses the use of incensole and or furanogermacrens,
     salts, metabolites and precursors thereof in the treatment of neoplasia,
     particularly resistant neoplasia and immunodysregulatory disorders.  These
     compds. can be administered alone or in combination with conventional
     chemotherapeutic, antiviral, antiparasite agents, radiation and/or
     surgery.  Incensole and furanogermacren and their mixt. showed antitumor
     activity against various human carcinomas and melanomas and antimicrobial
     activity against Staphylococcus aureus and Enterococcus faecalis.

L10  ANSWER 3 OF 12  EMBASE  COPYRIGHT 2003 ELSEVIER SCI. B.V.
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Blossom Street WEL224, Boston, MA 02114-2698, United States. hasan@helix.mgh.harvard.edu. Cancer Research 61/11 (4490-4496) 1 Jun 2001.
Refs: 45.
ISSN: 0008-5472. CODEN: CNREA8. Pub. Country: United States. Language: English. Summary Language: English.

AB Immunophotodiagnosis uses a fluorescence-labeled monoclonal **antibody** (MAb) that recognizes a tumor-associated antigen to image the fluorescence emitted from the fluorophore-bound MAb that has localized in the tissue. It may be used to diagnose malignant or precancerous lesions, to delineate the margins for tumor resection, or as a feedback mechanism to assess response to treatment. In oral precancer, the epidermal growth factor **receptor** (EGFR) is overexpressed and could be used as a marker for early detection or as a target for therapy. The goal of this study was to test an anti-EGFR MAb (C225) coupled to either the near-infrared fluorescent dye N,N'-di-carboxypentyl-indodicarbocyanine-5,5' disulfonic acid for detection or a photochemically active dye (**chlorin**(e6)) for therapy of early premalignancy in the hamster cheek pouch carcinogenesis model. Fluorescence levels in the carcinogen-treated tissue correlated with the histological stage of the lesions when the C225-N,N'-di-carboxypentyl-indodicarbocyanine-5,5'-disulfonic acid conjugate was used but did not do so with the irrelevant conjugates. Discrete areas of clinically normal mucosa with high fluorescence (hot spots) were subsequently shown by histology to contain dysplastic areas. The best contrast between normal and carcinogen-treated cheek pouches was found at 4-8 days after injection. To test the potential of immunophotodiagnosis as a feedback modality for therapeutic intervention, experiments were conducted with the same MAb conjugated to chlorines followed by illumination to reduce expression of the EGFR by a photodynamic effect. Subsequent immunophotodiagnosis showed that this treatment led to a significant reduction in fluorescence in the carcinogen-treated cheek pouch compared with nonilluminated areas. This difference between illuminated and dark areas was not seen in the normal cheek pouch. Taken together, the results demonstrate the potential for development of immunophotodiagnosis as a diagnostic tool and as a method of monitoring response to therapy and that the EGFR may be an appropriate target in head and neck cancer.

L10 ANSWER 4 OF 12 CAPLUS COPYRIGHT 2003 ACS
2000:496418 Document No. 133:101471 Transcutaneous photodynamic treatment of targeted cells. Chen, James (Light Sciences, Ltd., USA). PCT Int. Appl. WO 2000041727 A1 20000720, 60 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US944 20000114. PRIORITY: US 1999-PV116234 19990114 ; US 1999-271575 19990318.

Ab The present invention is drawn to methods and compds. for photodynamic therapy (PDT) of a target tissue or compns. in a mammalian subject, using a light source that preferably transmits light to a treatment site transcutaneously. The method provides for administering to the subject a therapeutically effective amt. of a targeted substance, which is either a targeted photosensitizing agent, or a photosensitizing agent delivery system, or a targeted prodrug. This targeted substance preferably

AB Photodynamic therapy (PDT) is based on the ability of porphyrins and some other photosensitizers (PSs) both to be accumulated preferentially in tumor cells and to generate singlet oxygen (O-1 2) when activated by visible light. However the selectivity of sensitizers towards tumor cells is not always sufficient for PDT to be efficient. In recent years targeted PDT (TPDT) has been developed in attempts to improve PS selective location in tumors by means of binding PSs to **targeting** (address) molecules such as **antibodies** (Abs), lectins, hormones, etc. In using TPDT, a new selectivity factor is added: high affinity of the **targeting** molecule for the respective tumor-associated antigen or **receptor**. This review deals with modern approaches to constructing targeted PSs (TPSs) as well as with the mechanism, prospects and limitations of TPDT application in the treatment of tumors.

L10 ANSWER 10 OF 12 SCISEARCH COPYRIGHT 2003 ISI (R) DUPLICATE 1
93:136178 The Genuine Article (R) Number: KP559. PHOTOPROPERTIES OF A MESOCHLORIN E6-N-(2 HYDROXYPROPYL)METHACRYLAMIDE COPOLYMER CONJUGATE. SPIKES J D (Reprint); KRINICK N L; KOPECEK J. UNIV UTAH, DEPT BIOL, SALT LAKE CITY, UT, 84112 (Reprint); UNIV UTAH, DEPT BIOENGN, SALT LAKE CITY, UT, 84112; UNIV UTAH, DEPT PHARMACEUT, SALT LAKE CITY, UT, 84112. JOURNAL OF PHOTOCHEMISTRY AND PHOTOBIOLOGY A-CHEMISTRY (15 FEB 1993) Vol. 70, No. 2, pp. 163-170. ISSN: 1010-6030. Pub. country: USA. Language: ENGLISH. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB In the photodynamic therapy (PDT) of tumors, improved efficiency of photosensitizer delivery to tumor cells and tumors can sometimes be obtained by binding them to monoclonal **antibodies** or other proteins, particulate materials, and certain types of synthetic water soluble polymers. Synthetic polymers are of particular interest as drug delivery carriers since **targeting** groups specific for surface markers on tumor cells can be attached to the polymer backbone increase the cellular uptake via **receptor**-mediated endocytosis. However, in many cases, the binding of sensitizers to macromolecules significantly alters their spectral and photosensitizing properties. This paper describes the effects of covalently binding the photosensitizer, mesochlorin e6 monoethylenediamine (CM), to a model N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer on its spectral, photophysical, photosensitizing and photobleaching properties in aqueous solution. Binding had little effect on the spectrum or triplet lifetime of CM, but significantly decreased the bimolecular quenching constant of oxygen for the **chlorin** triplet. Binding also reduced the quantum yield of singlet oxygen production by illuminated CM from 0.73 to 0.25. Photo-oxidation efficiencies for furfuryl alcohol and certain biomolecules were also decreased. Addition of a cationic detergent to the CM-HPMA copolymer increased the yield of singlet oxygen production and the photosensitizing efficiency up to the levels of the free sensitizer. Binding CM to the HPMA copolymer significantly increased its resistance to photobleaching.

L10 ANSWER 11 OF 12 EMBASE COPYRIGHT (C) 2003 ELSEVIER SCI. B.V.DUPLICATE 2
96106446 EMBASE Document No.: 1996106446. Targetable photoactivatable drugs. 1. In vitro efficacy of polymer bound **chlorin** e6 toward human hepatocarcinoma cell line (HLE/PAF/3) targeted with galactosamine and to mouse splenocytes targeted with anti-Thy 1.2 **antibodies**. Rihova B.; Krinick N.L.; Kopecek J.. Institute of Microbiology, Czech Republic Academy of Sciences, 14220 Prague 4, Czech Republic. Journal of Controlled Release 25/1-2 (71-87) 1993.
ISSN: 0168-3659. CODEN: JCREEC. Pub. Country: Netherlands. Language: English. Summary Language: English.

on the human hepatocarcinoma cell line PLC/PRF/5 and the anti-Thy 1.2 **antibody** interacts with Thy 1.2 alloantigens on mouse splenic T cells. The efficiency of photodynamic injury as a function of incubation time and temperature, and irradiation time was studied. Two-day-old cultures of PLC/PRF/5 cell line were most sensitive to HPMA copolymer bound **chlorin** e6 (targeted or nontargeted), whereas no differences were observed when free drug was tested on 1-, 2- or 3-day-old cultures. Dark toxicity of the free drug was observed at concentrations as low as 2 x 10-6 M. Dark toxicity decreased when **chlorin** e6 was bound to HPMA copolymers, especially to conjugates containing **targeting** moieties. The effect of incubation time was seen only in the hepatocarcinoma cell culture. For galactosamine-targeted HPMA copolymer bound **chlorin** e6, 2-3 h were necessary to induce a pronounced killing effect. For anti-Thy 1.2 targeted polymeric drug and for free **chlorin** e6, 1 h of incubation was sufficient to load the cells with a photolytic dose of **chlorin** e6. Dependence on the time of irradiation was observed in both targeted conjugates. One hour of irradiation induced only limited photolysis, whereas 7.5 h of irradiation was necessary for substantial photodynamic injury. Photodynamic destruction of cells exposed to free drug was similar for irradiation periods of 1-7.5 h. In accordance with the mechanism of cellular uptake of polymeric conjugates by **receptor**-mediated endocytosis, the conjugates were less photodynamically active when incubated with cell cultures at a lower (4.degree.C) temperature. Nontargeted polymeric **chlorin** e6 was always considerably less phototoxic when compared to targeted HPMA copolymer conjugates. **Antibody** response to thymus-dependent antigen (SRBC) induced in vitro is more sensitive to the targeted photosensitizer, if compared with the estimation of cell viability. It suggests that lower concentrations of the photosensitizer do not destroy (disintegrate) the target cells, but their function and/or proliferation may be impaired. Binding of **antibodies** via carbohydrate moieties in the Fc portion of the anti-Thy 1.2 molecule increases the photodestructive capacity of the **antibody** targeted photosensitizer, when compared to conjugates where the **antibody** was bound via N(.epsilon.)-amino groups of lysine residues. A concentration of 1 x 10-7 M of **chlorin** e6 in the former conjugate kills 40 , and a concentration of 1 x 10-8 M 30 of target T cells while the latter conjugate and free drug are ineffective at the above mentioned concentrations. The results obtained from these two in vitro models allowed us to compare the photodynamic effect of targeted HPMA copolymer bound **chlorin** e6 on a hepatocarcinoma cell line (model of anticancer treatment) and on normal lymphocytes (model of immunosuppression).

L10 ANSWER 12 OF 12 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3

91203374 EMBASE Document No.: 1991203374. Targetable photoactivatable polymeric drugs. Kopecek J.; Rihova B.; Krinick N.L.. University of Utah, CCRD, 421 Wakara Way,Salt Lake City, UT 84.., United States. Journal of Controlled Release .16/1-2 (137-144) .1991.
ISSN: 0168-3659. CODEN: JCREEC. Pub. Country: Netherlands. Language: English. Summary Language: English.

Ab The design of targetable polymeric photoactivatable drugs based on N-(2-hydroxypropyl) methacrylamide (HPMA) copolymers is described. Two types of conjugates have been synthesized: (a) HPMA copolymer-galactosamine-**chlorin** e6 conjugates; and (b) HPMA copolymer-anti-Thy 1.2 **antibody**-**chlorin** e6 conjugates. Their photodynamic activity was evaluated in vitro. The conjugate containing galactosamine as the **targeting** moiety was tested on a

copolymer-anti-Thy 1.2 **antibody**-**chlorin** e6 conjugates was evaluated towards mouse splenocytes in vitro. They differ in the method of **antibody** binding. One contained anti-Thy 1.2 **antibodies** bound via N(.epsilon.)-amino groups of lysine residues, the other contained anti-Thy 1.2 **antibodies** bound via oxidized carbohydrate groups. Both targetable conjugates were more biologically active when compared to a nontargetable HPMA copolymer-**chlorin** e6 conjugate. The conjugate which contained anti-Thy 1.2 **antibodies** bound via carbohydrate groups was the most active both in its photodynamic effect on the viability of splenocytes and the suppression of the primary **antibody** response of mouse splenocytes towards sheep red blood cells in vitro.

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L12 69 L11 AND PHOTODYNAMIC THERAPY

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PROCESSING COMPLETED FOR L12
L13 44 DUP REMOVE L12 (25 DUPLICATES REMOVED)

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L13 ANSWER 1 OF 44 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:594435 Document No.: PREV200200594435. Patient portable device for **photodynamic therapy**. **Chen, James (1)**; Wilkerson, Brian; Brown, Dave; Huston, Darrin; McQuade, Mike. (1) Bellevue, WA USA. ASSIGNEE: Light Science Corporation, Issaquah, WA, USA. Patent Info.: US 6454789 September 24, 2002. Official Gazette of the United States Patent and Trademark Office Patents, (Sep. 24, 2002) Vol. 1262, No. 4, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133. Language: English.

AB A patient portable **photodynamic therapy** device securable to a patient includes a lightweight rechargeable battery and a cold cathode fluorescent (CCF) tube powered thereby. The CCF tube is coupled in light channeling relation to a proximal portion of a biocompatible optical fiber, which includes a distal portion with an optional diffuser that uniformly distributes light as it exits the distal portion. The distal end of the optical fiber is optionally provided with an anchoring balloon that can be inflated after the optical fiber is properly positioned at a treatment site within a patient's body. The balloon securely lodges the distal portion within the tissue at the treatment site, and is deflated to facilitate the removal of the optical fiber once the treatment is complete.

L13 ANSWER 2 OF 44 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:[illegible] Document No.: PREV[illegible]. Application of light at plural treatment sites within a tumor to increase the efficacy of light therapy. **Chen, James C.**. ASSIGNEE: Light Science Corporation. Patent Info.: US 6416531 July 9, 2002. Official Gazette of the United States Patent and Trademark Office Patents, (July 9, 2002) Vol. 1260, No. 2, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133. Language: English.

AB Light is administered during **photodynamic therapy** (PDT) for an extended period of time at a plurality of sites distributed

this process, a plurality of light emitting optical fibers or probes are deployed in a spaced-apart array. After a photoreactive agent is absorbed by the abnormal tissue, the light therapy is administered for at least three hours. The greater volume of necrosis in the tumor is achieved due to one or more concomitant effects, including: the inflammation of damaged abnormal tissue and resultant immunological response of the patient's body; the diffusion and circulation of activated photoreactive agent outside the expected fluence zone, which is believed to destroy the abnormal tissue; a retrograde thrombosis or vascular occlusion outside of the expected fluence zone; and, the collapse of the vascular system that provides oxygenated blood to portions of the tumor outside the expected fluence zone. In addition, is possible that molecular oxygen diffusing and circulating into the expected fluence zone is converted to singlet oxygen during the extended light therapy, causing a gradient of hypoxia and anoxia that destroys the abnormal tissue outside the expected fluence zone.

L13 ANSWER 3 OF 44 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:174072 Document No.: PREV200200174072. Use of pegylated photosensitizer conjugated with an antibody for treating abnormal tissue. **Chen, James C.**. ASSIGNEE: Light Sciences Corporation. Patent Info.: US 6344050 February 05, 2002. Official Gazette of the United States Patent and Trademark Office Patents, (Feb. 5, 2002) Vol. 1259, No. 1, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133. Language: English.

AB A photosensitizer suitable for use in administering **photodynamic therapy** (PDT), conjugated with antibodies that are targeted to antigens on abnormal tissue and polyethylene glycol (PEG) or other polymer that extends the residence time of the conjugate within a patient's body. The resulting pegylated targeted conjugate is administered to a patient, and after the antibodies have had sufficient time to bind with the antigens, light from an external or internal source having a waveband corresponding to an absorption waveband of the photosensitizer is administered. Use of an external light source that emits relatively long wavelength light enables the light to pass through any intervening dermal layer and normal tissue between the external light source and the treatment site. Since the photosensitizer in the conjugate is bound to the abnormal tissue, the light therapy has minimal effect on the intervening normal tissue. Furthermore, the efficacy of the PDT is enhanced due to the increased concentration of the photosensitizer of the conjugate linked to the abnormal tissue.

L13 ANSWER 4 OF 44 CAPLUS COPYRIGHT 2003 ACS
2002:696468 Document No. 137:206636 Use of photoluminescent nanoparticles for **photodynamic therapy**. **Chen, James** (USA). U.S. Pat. Appl. Publ. US 2002127224 A1 20020912, 25 pp. (English). CODEN: USXXCO. APPLICATION: US 2001-91144 20020304. PRIORITY: US 2001-PV272877 20010302.

AB Disclosed are compns. and methods that can be used to effect a **photodynamic therapy** (PDT) such as cancer treatment or gene transcription. Compns. include light-emitting nanoparticles that absorb light of one wavelength emitted by a light source and emit light of another wavelength that activates a PDT drug. Light-emitting nanoparticles include quantum dots, nanocrystals, and quantum rods as well as mixts. of these nanoparticles. The nanoparticles may be delivered to a patient in a liq. carrier or as part of a solid carrier such as a biocompatible polymeric film, a polymeric sheath, or other carrier suitable for introduction at the site to be treated. In one embodiment of

linkage group that has affinity for e.g. cells or proteins produced at the site to be treated. A sufficient no. of light-emitting nanoparticles are delivered to the treatment site to activate the PDT drug and effect treatment.

L13 ANSWER 5 OF 44 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
2002323076 EMBASE Synthesis of a water-soluble cyclodextrin modified hypocrellin and ESR study of its **photodynamic therapy** properties. Gu Z.-Z.; **Chen J.-R.**; Wang X.-S.; Zhang B.-W.; Cao Y.; Z.-Z. Gu, Tech. Inst. of Physics and Chemistry, Chinese Academy of Sciences, Beijing 100101, China. g205@ipc.ac.cn. New Journal of Chemistry 26/9 (1132-1136) 2002.
Refs: 38.
ISSN: 1144-0546. CODEN: NJCHE5. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB A water-soluble cyclodextrin modified hypocrellin B (HBCD) was designed and synthesized. HBCD retained the phototherapeutic properties and exhibited much stronger photoinduced damage to calf thymus DNA (CT DNA) than hypocrellin B and mercaptoacetic acid substituted hypocrellin B (MAHB). The mechanism of electron transfer from CT DNA to the triplet state of HBCD was confirmed by steady-state electron spin resonance (ESR) and a time-resolved ESR study.

L13 ANSWER 6 OF 44 MEDLINE DUPLICATE 2
2002440990 Document Number: 22187159. PubMed ID: 12198571. Comparison of 5-aminolevulinic acid and its hexylester mediated photodynamic action on human hepatoma cells. Ren Qing-Guang; Wu Su-Min; Peng Qian; **Chen Ji-Yao**. (Department of Physics, Fudan University, Shanghai 200433, China.. jychen@fudan.edu.cn) . Sheng Wu Hua Xue Yu Sheng Wu Wu Li Xue Bao (Shanghai), (2002 Sep) 34 (5) 650-4. Journal code: 26730160R. ISSN: 0582-9879. Pub. country: China. Language: English.
AB 5-Aminolevulinic acid (ALA) is a precursor to heme synthesis pathway and currently used to induce endogenous protoporphyrin IX (PpIX, a potent photosensitizer) for **photodynamic therapy** of cancer.
ALA has, however, a limited ability to cross cellular membranes due to its low lipid solubility. The use of lipophilic ALA esters may increase cellular uptake, which results in an enhanced PpIX synthesis. In the present study, a comparison of ALA and its hexyl ester (He-ALA) was made in the QGY human hepatoma cell line with respect to PpIX production and its photocytotoxicity. The fluorescence emission spectrum of the cells incubated with He-ALA was identical to that of PpIX, indicating that He-ALA could induce PpIX in the cells. Fluorescence images demonstrated that the He-ALA induced PpIX was localized in the cytoplasm of the cells. Moreover, a similar amount of Pp IX was found in the cells incubated with 0.2 mmol/L He-ALA or 2 mmol/L ALA and a similar level of cell survival was reached following light exposure. These results suggest that He-ALA is much more efficient at producing PpIX and photocytotoxicity than ALA itself in the cells.

L13 ANSWER 7 OF 44 CAPLUS COPYRIGHT 2003 ACS
2002:94291 The effects of ALA-PDT on leukemia cells and hepatoma cells. **Chen, Ji-Yao**; Ren, Qing Guang; Wu, Su-Min; Wang, Lei-Ming (Department of Physics, Fudan University, Shanghai, Peop. Rep. China). Journal of Photoscience, 9(2), 512-514 (English) 2001. CODEN: JOPHFS. ISSN: 1225-8555. Publisher: Korean Society of Photoscience.
AB 5-aminolevulinic acid (ALA) is a new kind drug used in **photodynamic therapy**. ALA-PDT have successfully used in superficial malignancies and some skin diseases. Here the effects of

hepatoma cells. The fluorescence images showed that the PpIX distribute in cytoplasm. However the efficiency of ALA photodynamic inactivation to two cell lines was different. The leukemia cells were more sensitive for ALA-PDT than hepatoma cells, revealing that the ALA-PDT effect is cell line dependent. However by using ALA-Hexyl ester (He-ALA) instead of ALA, the cell photo-inactivation was improved. The PDT efficiency of He-ALA was 10 times high than that of ALA, showing He-ALA is a very promising drug in ALA-PDT.

L13 ANSWER 9 OF 44 CAPLUS COPYRIGHT 2002 ACS
2002:130969 Document No. 136:[illegible] Metal ions affect on the photodynamic actions of cyclodextrin-modified hypocrellin. Gu, Zhi-Ze; **Chen, Jing-Rong;** Wang, Xue-Song; Zhang, Bao-Wen; Cao, Yi (Technical Institute of Physics and Chemistry, Chin. Academy of Sciences, Beijing, 100101, Peop. Rep. China). Chemistry Letters (2), 206-207 (English) 2002. CODEN: CMLTAG. ISSN: 0366-7022. Publisher: Chemical Society of Japan.
AB Cu2+, Fe2+ and Fe3+ chelate with cyclodextrin-modified hypocrellin (HBCD) efficiently and the UV-visible spectra of the resultant metal complexes red shifts by more than 40 nm, enhancing the absorbance of HBCD in the phototherapeutic window. ESR study revealed that the hydroxyl radical was the main product during irradn. of these metal complexes because Cu2+, Fe2+ and Fe3+ initiated the Fenton reaction. Also, these metal complexes photodamaged calf thymus DNA in a liposome system 20 fold faster than in a buffer soln. due to the initiation of lipid peroxidn.

L13 ANSWER 9 OF 44 SCISEARCH COPYRIGHT 2002 ISI (R) DUPLICATE 5
2002:376175 The Genuine Article (R) Number: 547JA. Diphenylchlorin and diphenylbacteriochlorin: synthesis, spectroscopy and photosensitising properties. Wang T Y; **Chen J R;** Ma J S (Reprint). Chinese Acad Sci, Inst Chem, Ctr Mol Sci, Beijing 100080, Peoples R China (Reprint); Chinese Acad Sci, Tech Inst Phys & Chem, Beijing 100101, Peoples R China. DYES AND PIGMENTS (MAR 2002) Vol. 52, No. 3, pp. 199-209. Publisher: ELSEVIER SCI LTD. THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND. ISSN: 0143-7208. Pub. country: Peoples R China. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS
AB Two new photosensitisers, diphenylchlorin and diphenylbacteriochlorin, were prepared from the reduction of 5,10-diphenylporphyrin. These dyes are characterised by strong light absorption in the red spectral region and afford high yields of photosensitised singlet oxygen, photosensitiser anion radicals, and superoxide anion radical, based on studies using EPR spectroscopy. Consequently, they are potential photosensitisers for **photodynamic therapy**. (C) 2002 Elsevier Science Ltd. All rights reserved.

L13 ANSWER 10 OF 44 MEDLINE DUPLICATE 6
2002212154 Document Number: 21944609. PubMed ID: 11999949. New technology for deep light distribution in tissue for phototherapy. **Chen James** ; Peltier Lloyd; Christophersen Celene; Zheng Frank; Krouse Michael; Singhal Anil; Wang Sylvia. Division of Science & Discovery, Light Sciences Corporation, Issaquah, Washington 98027, USA. (CANCER JOURNAL, (2002 Mar-Apr) 8 (2) 154-63. Journal code: 11608-1951. ISSN: 1528-9117. Pub. country: United States. Language: English.
AB **Photodynamic therapy** is one of several techniques developed for phototherapy for solid cancers and hematologic malignancies. **Photodynamic therapy** is a treatment that utilizes a molecular energy exchange between visible light and a photosensitive drug, which results in the production of 1O2, a highly reactive cytocidal oxygen

dye-pumped or diode lasers. The cost and the complexity of lasers have seriously limited the clinical use of **photodynamic therapy** for malignancies. A new device technology, based on light-emitting diodes, has been developed (Light Sciences Corporation, Issaquah, WA) that allows light production inside the target tissue. This new technology will expand the current range of indications that are treatable with **photodynamic therapy** to include moderate- and large-volume refractory tumors. Conventional **photodynamic therapy** utilizes the delivery of intense light for seconds or minutes. The new approach differs from conventional **photodynamic therapy** in that it combines a novel interstitial light delivery system with prolonged photoactivation of photosensitive drugs. Prolonging photoactivation time in order to deliver a higher light dose results in an amplification effect, whereby the repeated activation of each photosensitive drug molecule leads to the generation of many thousands of ROS molecules. The production of overwhelming numbers of these powerful oxidants in individual cells and the vascular supply of tumors leads to irreversible damage and death of the targeted lesions. Results of preclinical studies have indicated a significant correlation between increased duration of photoactivation and increased volume and depth of **photodynamic therapy** -induced necrosis. The new developments will enable **photodynamic therapy** to be used effectively against refractory bulky disease as frontline therapy or in combination with chemotherapy, radiation therapy, or biologics. Perhaps most promising, many patients with advanced refractory disease may now be relieved of symptoms or may return to the treatable population.

L13 ANSWER 11 OF 44 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2001:531916 Document No.: PREV200100531916. Real-time monitoring of **photodynamic therapy** over an extended time. **Chen, James C.**. ASSIGNEE: Light Sciences Corporation. Patent Info.: US 6238426 May 29, 2001. Official Gazette of the United States Patent and Trademark Office Patents, (May 29, 2001) Vol. 1246, No. 5, pp. No Pagination. e-file. ISSN: 0098-1133. Language: English.

AB Progress of **photodynamic therapy** (PDT) administered over an extended period of time is monitored using an ultrasonic probe, which produces ultrasound images of an internal treatment site in real time. The ultrasound images indicate the extent and volume of an infarction zone within a tumor or other diseased tissue at the internal treatment site within a patient's body. Light is administered to the internal treatment site from either an internal or external light source that produces light in a wavelength corresponding to the characteristic absorption wavelength a photoreactive agent that is administered to a patient. Prior to or shortly after initiating administration of the light therapy, a baseline ultrasound image is produced for comparison to subsequent ultrasound images made after the effects of the PDT on the diseased tissue have occurred. By evaluating changes in the internal treatment site shown in the ultrasound images during the progress of the PDT, the intensity and/or duration of intervals of light being administered to the patient can be varied, and/or terminated at an appropriate time, thereby minimizing risk of harm to normal tissue surrounding the internal treatment site. Light is delivered from an external laser source through an optical fiber, or through an implanted light probe that includes one or more light emitting sources, or by an external array of light emitting diodes that emit light of sufficiently long wavelength to penetrate a dermal layer into the internal treatment site.

USA). PCT Int. Appl. WO 2001015694 A1 20010308, 62 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO 2000-US24120 20000831. PRIORITY: US 1999-388092 19990831.

AB The present invention is drawn to methods and compds. for **photodynamic therapy** (PDT) of a target tissue or compns. in a mammalian subject, using a light source that preferably transmits light to a treatment site transcutaneously. The method provides for administering to the subject a therapeutically effective amt. of a photosensitizing agent. This photosensitizing agent preferentially assocs. with the target tissue. Light at a wavelength or waveband corresponding to that which is absorbed by the photosensitizing agent is then administered. The light intensity is relatively low, but a high total fluence is employed to ensure the activation of the photosensitizing agent. Transcutaneous PDT is useful in the treatment of specifically selected target tissues, such as vascular endothelial tissue, the abnormal vascular walls of tumors, solid tumors of the head and neck, tumors of the gastrointestinal tract, tumors of the liver, tumors of the breast, tumors of the prostate, tumors of the lung, nonsolid tumors, malignant cells of the hematopoietic and lymphoid tissue and other lesions in the vascular system or bone marrow, and tissue or cells related to autoimmune and inflammatory disease.

L13 ANSWER 13 OF 44 SCISEARCH COPYRIGHT 2003 ISI (R)

2001:691352 The Genuine Article (R) Number: 464EP. The synthesis of chlorophyll derivatives and their photosynthetic activities in purple bacteria reaction centers. Chen S L (Reprint); **Chen J R**; Zou Y L; Wu Y L; Deng X H; Xu C H. Mil Med Coll 2, Fac Naval Med, Shanghai 200433, Peoples R China (Reprint); Chinese Acad Sci, Shanghai Inst Plant Physiol, Shanghai 200032, Peoples R China; Chinese Acad Sci, Shanghai Inst Organ Chem, Shanghai 200032, Peoples R China. ACTA CHIMICA SINICA (AUG 2001) Vol. 59, No. 8, pp. 1310-1316. Publisher: SCIENCE PRESS, 16 DONGHUANGCHENGGEN NORTH ST, BEIJING 100717, PEOPLES R CHINA. ISSN: 0567-7351. Pub. country: Peoples R China. Language: Chinese. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Chlorophyll derivatives were synthesized and five of them were reported for the first time. In the presence of acetone and an excess of exogenous plant pheophytins, bacteriopheophytins in the reaction centers from Rhodobacter sphaeroides RS601 were replaced by the pheophytins at sites H-A and H-B. When incubated at 43.5 degreesC for 60 min, the photochemical activities of the pheophytin reaction center are 71.4% of the control. The electron transfer rate of Bphe(-), Bphe(plus)-/phe(-) and Q(A)(-) over Bur /Q(A) was decreased.

L13 ANSWER 14 OF 44 SCISEARCH COPYRIGHT 2003 ISI (R) DUPLICATE 5

2001:500866 The Genuine Article (R) Number: 463YL. Synthesis and **photodynamic therapy** properties of a water-soluble hypocrellin modified by cyclodextrin. Gu Z G; **Chen J R**; Wang X J; Zhang B W (Reprint); Cao Y. Chinese Acad Sci, Tech Inst Phys & Chem, Beijing 100101, Peoples R China (Reprint). CHEMISTRY LETTERS (5 AUG 2001) No. 8, pp. 858-859. Publisher: CHEMICAL SOC JAPAN, 1-5 KANDA-SURUGADAI CHIYODA-KU, TOKYO, 101, JAPAN. ISSN: 0366-7022. Pub. country: Peoples R

resonance (ESR) measurement indicated that this HB derivative remained photodynamically active in terms of type I and type II mechanisms. HBCD is water-soluble and possesses stronger photosensitized damage ability to calf thymus DNA than hypocrellin B.

L13 ANSWER 15 OF 44 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 6
2001070953 EMBASE Endogenous production of protoporphyrin IX induced by 5-aminolevulinic acid in leukemia cells. **Chen J.-Y.**; Mak N.-K.; Cheung N.-H.; Leung P.-K.; Peng Q.. Dr. J.-Y. Chen, Department of Physics, Fudan University, Shanghai 200433, China. jychen@fudan.edu.cn. Acta Pharmacologica Sinica 22/2 (163-168) 2001.
Refs: 13.
ISSN: 0253-9756. CODEN: CYLPDN. Pub. Country: China. Language: English. Summary Language: English; Chinese.
AB AIM: To explore the photosensitization of 5-aminolevulinic acid (ALA) in myeloid leukemia cell line. METHODS: Using the technique of fluorescence spectra, the ALA induced protoporphyrin IX (PpIX) was measured in myeloid leukemia JOS cells. Confocal laser scanning microscopy (CLSM) combined with fluorescence organelle probe was used to detecte the localization of PpIX in JOS cells at the subcellular levels. MTT assay was used to measure the cell survival after light irradiation. RESULTS: ALA successfully produced endogenous PpIX in leukemia JOS cells. PpIX was observed to be distributed in the cytoplasm and mitochondria was exhibited as the one of binding sites of PpIX. As a photosensitizer, PpIX initiated photodynamic reaction after light irradiation and effectively photodamaged leukemia cells. CONCLUSION: ALA-based photosensitization could be used for inactivation of leukemia cells.

L13 ANSWER 16 OF 44 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 7
2001340114 EMBASE **Photodynamic therapy** for patients with advanced non-small-cell carcinoma of the lung. Jones B.U.; Helmy M.; Brenner M.; Serna D.L.; Williams J.; **Chen J.C.**; Milliken J.C.. Dr. J.C. Milliken, UC Irvine Medical Center, Division of Cardiothoracic Surgery, The University of California, 101 The City Drive, Orange, CA 92868, United States. jcmilliken@uci.edu. Clinical Lung Cancer 3/1 (37-41) 2001.
Refs: 19.
ISSN: 1525-7304. CODEN: CLCLCA. Pub. Country: United States. Language: English. Summary Language: English.
AB Patients with advanced non-small-cell lung carcinoma (NSCLC) have poor prognoses and experience negative sequelae of disease. Patients often suffer from dyspnea and/or hemoptysis, with overall pulmonary compromise. Patients with advanced, inoperable disease have limited options for treatment. This study summarizes our early experience and findings using **photodynamic therapy** (PDT) as an effective modality in the palliation of hemoptysis, dyspnea, and physical airway obstruction in cases of inoperable lung cancer. A retrospective review was conducted for the first 10 patients diagnosed with stage III/IV obstructive NSCLC who underwent PDT at our institution. Endobronchial lesions were identified by bronchoscopy. Treatments were initiated 48 hours after intravenous injection of 2 mg/kg of the photosensitizing agent porfimer sodium (Photofrin, QLT PhotoTherapeutics, Vancouver, BC). The porfimer sodium was then activated by illumination with a 630 nm wavelength light using a coherent argon ion laser through a flexible bronchoscope. Repeated bronchoscopies were performed 1-3 days following initial PDT for evaluation and airway debridement. In 8 cases, a second treatment of PDT was administered within 72 hours of the first injection. One patient received a third treatment several months later. Three patients also

months post-PDT, while median survival postdiagnosis was 10.5 months. Three patients are alive at the time of this review at 5-21 months following therapy. Patients with unresectable late-stage NSCLC have few options for treatment. Our early experience with PDT indicates effective relief of hemoptysis, dyspnea, and airway obstruction and improves their quality of life.

L13 ANSWER 17 OF 44 CAPLUS COPYRIGHT 2003 ACS
2000:493416 Document No. 133:101471 Transcutaneous photodynamic treatment of targeted cells. **Chen, James** Light Sciences, Ltd., USA). PCT Int. Appl. WO 2000041727 A1 20000720, 63 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US944 20000114. PRIORITY: US 1999-PV116234 19990115; US 1999-271575 19990318.

AB The present invention is drawn to methods and compds. for **photodynamic therapy** (PDT) of a target tissue or compns. in a mammalian subject, using a light source that preferably transmits light to a treatment site transcutaneously. The method provides for administering to the subject a therapeutically effective amt. of a targeted substance, which is either a targeted photosensitizing agent, or a photosensitizing agent delivery system, or a targeted prodrug. This targeted substance preferably selectively binds to the target tissue. Light at a wavelength or waveband corresponding to that which is absorbed by the targeted substance is then administered. The light intensity is relatively low, but a high total fluence is employed to ensure the activation of the targeted photosensitizing agent or targeted prodrug product. Transcutaneous PDT is useful in the treatment of specifically selected target tissues, such as vascular endothelial tissue, the abnormal vascular walls of tumors, solid tumors of the head and neck, tumors of the gastrointestinal tract, tumors of the liver, tumors of the breast, tumors of the prostate, tumors of the lung, nonsolid tumors, malignant cells of the hematopoietic and lymphoid tissue and other lesions in the vascular system or bone marrow, and tissue or cells related to autoimmune and inflammatory disease.

L13 ANSWER 16 OF 44 CAPLUS COPYRIGHT 2003 ACS
2000:493416 Document No. 133:109963 Noninvasive vascular **photodynamic therapy**. **Chen, James** (Light Sciences, Ltd., USA). PCT Int. Appl. WO 2000041726 A2 20000720, 28 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. English. CODEN: PIXXD2. APPLICATION: WO 2000-US852 20000114. PRIORITY: US 1999-PV116235 19990115.

AB The present invention is drawn to methods and compds. for transcutaneous **photodynamic therapy** ("PDT") of a target tissue or compns. in a mammalian subject, which includes administering to the subject a therapeutically effective amt. of a photosensitizing agent or a

photosensitizing agent or if prodrug, by a prodrug product thereof, where the light is provided by a light source, and where the irradn. is at low fluence rate that results in the activation of the photosensitizing agent or prodrug product. These methods of transcutaneous PDT are useful in the treatment of specifically selected target tissues, such as: vascular endothelial tissue; abnormal vascular wall of tumors; tumors of the head and neck; tumors of the gastrointestinal tract; tumors of the liver; tumors of the esophopharyngeal; tumors of the lung; lymphoid tissue; lesions in the vascular system; bone marrow and tissue related to autoimmune disease.

L13 ANSWER 19 OF 44 CAPLUS COPYRIGHT 2005 ACS
2000:493415 Document No. 133:101470 Compositions and methods for the treatment of metabolic bone disorders and bone metastases. **Chen, James** (Light Sciences, Ltd., USA). PCT Int. Appl. WO 2000041725 A2 20000720, 87 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, GY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US648 20000114. PRIORITY: US 1999-PV116133 19990115.

AB The present invention is drawn to methods and compns. useful for targeting and treating target tissues affected by or involved in metabolic bone disorders and bone metastases with **photodynamic therapy** (PDT) in a mammalian subject. The compns. are bisphosphonates, pyrophosphates or bisphosphonate-like compds. conjugated to photosensitive agents which are optionally further conjugated to ligands which are target tissue specific antibodies, peptides or polymers. The methods of PDT treatment utilize these compns. to target the tissues or cells of a mammalian subject to be treated. The methods comprise irradiating at least a portion of the subject with light at a wavelength absorbed by said photosensitizing agent that under conditions of activation during **photodynamic therapy** using a relatively low fluence rate, but an overall high total fluence dose results in minimal collateral tissue damage.

L13 ANSWER 20 OF 44 CAPLUS COPYRIGHT 2005 ACS
2000:441575 Document No. 133:63979 PEGylated photosensitizers for abnormal tissue treatment. **Chen, James C.** (Light Sciences Limited Partnership, USA). PCT Int. Appl. WO 2000036983 A1 20000629, 24 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US30530 19991207. PRIORITY: US 1998-218336 19981221.

AB A photosensitizer suitable for use in administering **photodynamic therapy** (PDT), conjugated with antibodies that are targeted to antigens on abnormal tissue, and PEG or other polymer that extends the residence time of the conjugate in vivo within a patient's body. The resulting pegylated targeted conjugate is administered to a patient, and after the antibodies have had sufficient time to bind with the antigens, light from an external or internal source having a waveband corresponding to an absorption waveband of the photosensitizer is administered. Use of an external light source that emits relatively long wavelength light enables the light to pass through any intervening dermal layer, and normal tissue between the external light source, and the treatment site. Since the photosensitizer in the conjugate is bound to the abnormal tissue, the

2000:521181 Document No.: PREV200000521181. The binding characteristics and intracellular localization of temoporfin (mTHPC) in myeloid leukemia cells: Phototoxicity and mitochondrial damage. **Chen, J. Y.**; Mak, N. K.; Yow, C. M. N.; Fung, M. C.; Chiu, L. C.; Leung, W. N.; Cheung, N. H. (1). (1) Department of Physics, Hong Kong Baptist University, 224 Waterloo Road, Kowloon, Hong Kong China. Photochemistry and Photobiology, October, 2000 Vol. 72, No. 4, pp. 541-547. print. ISSN: 0031-8655. Language: English. Summary Language: English.

AB The state of aggregation of the photosensitizer meso-tetrahydroxyphenylchlorin (mTHPC) in both cell free and intracellular environment was elucidated by comparing its absorption and excitation spectra. In methanol, mTHPC existed as monomers and strongly fluoresced. In aqueous solutions such as phosphate-buffered saline (PBS), mTHPC formed nonfluorescent aggregates. Some portion of mTHPC monomerized in the presence of 10% fetal calf serum PBS. In murine myeloid leukemia M1 and WEHI-3B (JCS) cells, cytoplasmic mTHPC were monomeric. By using organelle-specific fluorescent probes, it was found that mTHPC localized preferentially at the mitochondria and the perinuclear region. Photodynamic treatment of mTHPC-sensitized leukemia cells caused rapid appearance of the apoptogenic protein cytochrome c in the cytosol. Results from flow cytometric analysis showed that the release of cytochrome c was especially pronounced in JCS cells, and well correlated with the extent of apoptotic cell death as reported earlier. Electron microscopy revealed the loss of integrity of the mitochondrial membrane and the appearance of chromatin condensation as early as 1 h after light irradiation. We conclude that rapid release of cytochrome c from photodamaged mitochondria is responsible for the mTHPC-induced apoptosis in the myeloid leukemia JCS and M1 cells.

L13 ANSWER 22 OF 44 SCISEARCH COPYRIGHT 2003 ISI (R)

2000:502127 The Genuine Article (R) Number: 328CV. Benzoporphyrin derivative monoacid ring A (Verteporfin) alone has no inhibitory effect on intimal hyperplasia: In vitro and in vivo results. Turnbull R C; **Chen J C**; Labow R S; Margaron P; Hsiang Y N (Reprint). UNIV BRITISH COLUMBIA, DEPT SURG, DIV VASC SURG, F128-2211 WESTBROOK MALL, VANCOUVER, BC V6T 2B5, CANADA (Reprint); UNIV BRITISH COLUMBIA, DEPT SURG, DIV VASC SURG, VANCOUVER, BC V6T 2B5, CANADA; UNIV OTTAWA, OTTAWA, ON, CANADA; QLT PHOTOTHERAPEUT INC, VANCOUVER, BC, CANADA. JOURNAL OF INVESTIGATIVE SURGERY (MAY-JUN 2000). Vol. 13, No. 3, pp. 153-159. Publisher: TAYLOR & FRANCIS INC. 325 CHESTNUT ST, SUITE 800, PHILADELPHIA, PA 19106. ISSN: 0894-1939. Pub. country: CANADA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Benzoporphyrin derivative monoacid ring A (Verteporfin, BPD-MA), a photosensitizing drug, has been suggested as having inhibitory effects on smooth muscle cell (SMC) proliferation in rabbit aortic intimal injuries. The effect of BPD-MA on vascular SMCs in the absence of light stimulation in vitro and in vivo was studied using models of intimal hyperplasia. Human SMCs were incubated with BPD-MA for 4 h in darkness. A small (20%) but significant decrease in viability ($n = 4$, $p < 0.05$) was noted for BPD-MA concentrations above 15 mg/mL. This was an all or none phenomenon with no further decrease in viability at higher concentrations. Treatment with BPD-MA was also carried out in vivo using a balloon injury model of intimal hyperplasia in rabbit aortas. Thirty-three rabbits were randomized into five groups and given intravenous BPD-MA (2 mg/kg) according to the following schedule: Group 1 ($n = 8$), BPD-MA 15 min prior to injury; Group 2 ($n = 8$), BPD-MA 15 min prior to injury plus a second dose 4 weeks later; Group 3 ($n = 4$), BPD-MA immediately postinjury; Group 4 ($n = 7$), BPD-MA immediately postinjury plus a second dose 4 weeks later; or Group 5 ($n =$

L13 ANSWER 23 OF 44 MEDLINE DUPLICATE 9
2000455957 Document Number: 20395982. PubMed ID: 10936672. Cellular uptake, subcellular localization and photodamaging effect of temoporfin (mTHPC) in nasopharyngeal carcinoma cells: comparison with hematoporphyrin derivative. Yow C M; **Chen J Y**; Mak N K; Cheung N H; Leung A W. (Department of Nursing and Health Sciences, Hong Kong Polytechnic University, Hong Kong.. hsnyow@polyu.edu.hk) . CANCER LETTERS, (2000 Sep 1) 157 (2) 123-31. Journal code: 7600053. ISSN: 0304-3835. Pub. country: Ireland. Language: English.

AB Temoporfin (meta-tetra (hydroxyphenyl)chlorin; mTHPC) potentiated a 100-fold higher cytotoxic effect than hematoporphyrin derivative (HPD) on two nasopharyngeal carcinoma cell lines (HK1 and CNE2) in terms of the overall **photodynamic therapy** (PDT) dose. The cellular uptake, evaluated by flow cytometry and spectrophotometry demonstrated that mTHPC exhibited higher uptake ability than HPD. Confocal laser scanning microscopy detection for both the sensitizer and mitochondria probe on the same cell images revealed that both drugs accumulated diffusely in the cytoplasm and that mitochondria is a target organelle. Photo-activation ruptured the mitochondria, with more pronounced mitochondrial damage being observed in mTHPC-PDT course. This correlated well with the cell photokilling efficiency of mTHPC.

L13 ANSWER 24 OF 44 SCISEARCH COPYRIGHT 2003 ISI (R) DUPLICATE 10
2000:545123 The Genuine Article (R) Number: 334MK. Subcellular localization of merocyanine 540 (MC540) and induction of apoptosis in murine myeloid leukemia cells. **Chen J Y**; Cheung N H; Fung M C; Wen J M; Leung W N; Mak N K (Reprint). HONG KONG BAPTIST UNIV, DEPT BIOL, 224 WATERLOO RD, KOWLOON, HONG KONG, PEOPLES R CHINA (Reprint); HONG KONG BAPTIST UNIV, DEPT BIOL, KOWLOON, HONG KONG, PEOPLES R CHINA; HONG KONG BAPTIST UNIV, DEPT PHYS, KOWLOON, HONG KONG, PEOPLES R CHINA; CHINESE UNIV HONG KONG, DEPT BIOL, HONG KONG, HONG KONG, PEOPLES R CHINA; FUDAN UNIV, DEPT PHYS, SHANGHAI 200433, PEOPLES R CHINA. PHOTOCHEMISTRY AND PHOTOBIOLOGY (JUL 2000) Vol. 72, No. 1, pg. 114-120. Publisher: AMER SOC PHOTOBIOLOGY. BIOTECH PARK, 1021 15TH ST, SUITE 9, AUGUSTA, GA 30901-3156. ISSN: 0031-8655. Pub. country: PEOPLES R CHINA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Subcellular localization of photosensitizers is thought to play a critical role in determining the mode of cell death after photodynamic treatment (PDT) of leukemia cells. Using confocal laser scanning microscopy and fluorescent organelle probes, we examined the subcellular localization of merocyanine 540 (MC540) in the murine myeloid leukemia M1 and WEHI 36 (JCS) cells. Two patterns of localization were observed: in JCS cells, MC540 was found to localize on the plasma membrane and mitochondria; and in M1 leukemia cells, MC540 was found to localize on lysosomes. The relationship between subcellular localization of MC540 and PDT-induced apoptosis was investigated. Apoptotic cell death, as judged by the formation of apoptotic nuclei, was observed 4 h after irradiation in both leukemia cell lines. Typical ladders of apoptotic DNA fragments were also detected by DNA gel electrophoresis in PDT-treated JCS and M1 cells. At the irradiation dose of 1.5 J/cm2 (LD50 for JCS and LD80 for M1 cells), the percentage of apoptotic JCS and M1 cells was 78 and 38%, respectively. This study provided substantial evidence that MC540 localized differentially in the mitochondria, and the subsequent photodamage of the organelle played an important role in PDT-mediated apoptosis in myeloid leukemia cells.

L13 ANSWER 25 OF 44 MEDLINE DUPLICATE 11
2000275382 Document Number: 20275382. PubMed ID: 10817631. Photocytotoxic

hscyow@polyu.edu.hk) . TOXICOLOGY LETTERS, (2000 Apr 10) 115 (1) 53-61. Journal code: 7709027. ISSN: 0378-4274. Pub. country: Netherlands. Language: English.

AB **Photodynamic therapy** (PDT) is a new approach to cancer treatment for a variety of malignant tumors. In this study, two clinical photosensitizers, Temoporfin (meta-tetra-hydroxyl-phenyl-chlorin; mTHPC) and merocyanine 540 (MC540), were selected to explore for their photocytotoxic and genotoxic effects on nasopharyngeal carcinoma cells (NPC/HK1 and CNE2). Results of tetrazolium reduction assay showed that 80% cell killing were achieved for both cell lines at 0.4 microg/ml mTHPC for 24 h incubation and then with 40 kJ/m2 light irradiation, whereas 40 microg/ml MC540 with 50 kJ/m2 light dosage was required to attain the same level of phototoxicity for NPC/HK1. On the contrary, NPC/CNE2 was quite resistant to MC540. Hence, mTHPC-mediated PDT exerted a more potent effect than MC540-mediated PDT, even though the molar extinction coefficient of the main absorption peak for MC540 is much higher than that of mTHPC. Dark cytotoxicity remained negligible for both sensitizers. Comet assay was used to evaluate the DNA strand break and potential genotoxic effect induced by mTHPC and MC540 on the NPC cells. No DNA strand break was detected in the absence of light, and under sublethal treatment (LD25) for either sensitizer-loaded cells. Confocal laser scanning microscopy showed that mTHPC and MC540 localized in the cytoplasm but not in the nucleus of the tumor cells, which provided evidence for undetectable DNA damage under dark and low photodynamic dose.

L13 ANSWER 26 OF 44 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2000:292165 Document No.: PREV200000292165. Radionuclide excited phosphorescent material for administering PDT. **Chen, James C.**. ASSIGNEE: Light Sciences Limited Partnership. Patent Info.: US 5997842 December 07, 1999. Official Gazette of the United States Patent and Trademark Office Patents, (Dec. 7, 1999) Vol. 1229, No. 1, pp. No pagination. e-file. ISSN: 0098-1133. Language: English.

AB Constructs including bars, capsules, beads, and sheets are configured with a radionuclide core that emits energetic particles activating a phosphorescent shell material surrounding the radionuclide core so that it emits light to administer light therapy or PDT. A biocompatible coating that is generally optically transparent encloses the radionuclide core and phosphorescent material to prevent a patient's body in which the constructs are disposed from being affected by any toxicity of the phosphorescent shell material. In a typical application of the constructs, a photoreactive agent is infused into the treatment site and selectively absorbed by abnormal tissue, for example, in a cancerous tumor. Light emitted by the phosphorescent material when activated by the energetic particles emitted from the radionuclide core administers **photodynamic therapy**, which destroys the abnormal tissue. Particularly, the beads, which are relatively small in size, can be targeted to abnormal tissue by providing a linking mechanism on the biocompatible coating so that the beads are coupled to antibodies found on the abnormal cells, but not on normal tissue. If a glass phosphor material that includes fused quartz or silica glass doped with metal ions is used for the phosphorescent shell material, the beads or other construct must be exposed to IR or other light, causing electrons that have been trapped inside the glass materials to combine with holes, emitting light of a shorter wavelength. The glass phosphor material is preferable, since it is substantially less toxic than other types of scintillators or phosphor materials.

L13 ANSWER 27 OF 44 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

5921244 Jul. 13, 1999. Official Gazette of the United States Patent and Trademark Office Patents, (Jul. 13, 1999) Vol. 1224, No. 2, pp. NO PAGINATION. ISSN: 0098-1133. Language: English.

L13 ANSWER 28 OF 44 CAPLUS COPYRIGHT 2003 ACS
1999:736502 Document No. 131:342187 Controlled activation of targeted radionuclides. **Chen, James C.** (Light Sciences Limited Partnership, USA). PCT Int. Appl. WO 9958149 A1 19991118, 24 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US9584 19990430. PRIORITY: US 1998-78629 19980513.

AB Abnormal tissue or malignant organelles within such tissue are destroyed by alpha particles emitted by radionuclide cores that are linked to the abnormal tissue. Targeted radionuclide beads each includes an alpha emitter radionuclide core to which a plurality of antibody linking sites are coupled. Surrounding the linking sites and radionuclide core is a polymeric shell that absorbs alpha particles emitted by the core. A reagent is applied to or included within the polymeric shell. Depending upon the material used for the reagent, it is activated by light of a particular waveband that is selectively applied after antibody linking sites on the exterior of the shell have linked the targeted radionuclide to abnormal tissue in the body of a patient. Certain reagents are activated by light in a waveband corresponding to an absorption waveband of the reagent, while other types of reagents are activated by ultrasonic energy applied from an ultrasound source. When thus activated, the reagent causes fragmentation of the polymeric shell, enabling the alpha particles to pass into the abnormal tissue to which the radionuclide core becomes linked. The alpha particles destroy the abnormal tissue. It is also contemplated that the radionuclide core may instead emit beta particles, which though less toxic than alpha particles, can still destroy the targeted abnormal tissue.

L13 ANSWER 29 OF 44 CAPLUS COPYRIGHT 2003 ACS
1999:672627 Document No. 131:291354 Radionuclide excited phosphorescent material for administering **photodynamic therapy**. **Chen, James C.** (Light Sciences Limited Partnership, USA). PCT Int. Appl. WO 9952565 A1 19991021, 28 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1999 US2003 19990129. PRIORITY: US 1998-59795 19980413.

AB Constructs including bars, capsules, beads, and sheets are configured with a radionuclide core that emits energetic particles activating a phosphorescent shell material surrounding the radionuclide core so that it emits light to administer light therapy or PDT. A biocompatible coating that is generally optically transparent encloses the radionuclide core and phosphorescent material to prevent a patient's body in which the constructs are disposed from being affected by any toxicity of the phosphorescent shell material. In a typical application of the constructs, a photoreactive agent is infused into the treatment site and selectively absorbed by abnormal tissue, for example, in a cancerous tumor. Light emitted by the phosphorescent material when activated by the energetic particles emitted from the radionuclide core administers **photodynamic therapy**, which destroys the abnormal tissue. Particularly, the beads, which are relatively small in size, can be targeted to abnormal tissue by providing a linking mechanism on the biocompatible coating so that the beads are coupled to antibodies found on the abnormal cells, but not on normal tissue. If a glass phosphor material that includes fused quartz or silica glass doped with metal ions

preferable, since it is substantially less toxic than other types of scintillators or phosphor materials.

L13 ANSWER 30 OF 44 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:128744 Document No.: PREV200200128744. Method and device for applying hyperthermia to enhance drug perfusion and efficacy of subsequent light therapy. **Chen, J. C.**; Wisniewski, B., Bellevue, Wash. USA.
ASSIGNEE: LIGHT SCIENCES LIMITED PARTNERSHIP. Patent Info.: US 5814003 Sept. 29, 1998. Official Gazette of the United States Patent and Trademark Office Patents, (Sept. 29, 1998) Vol. 1214, No. 5, pp. 3154. ISSN: 0098-1133. Language: English.

L13 ANSWER 31 OF 44 CAPLUS COPYRIGHT 2003 ACS
1998:744945 Document No. 130:1648 Internal two photon excitation device for delivery of PDT to diffuse abnormal cells. **Chen, James C.**; Wisniewski, Brent (Light Sciences Limited Partnership, USA). PCT Int. Appl. WO 9850034 A1 19981112, 29 pp. DESIGNATED STATES: W: AU, CA, JP; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1998-US7726 19980415. PRIORITY: US 1997-850909 19970505.
AB A plurality of light sources that emit light having a long wavelength are energized for an extended period of time to increase the likelihood of two photon absorption by cells that have preferentially absorbed a photoreactive agent such as psoralen. The cells are preferably microscopic metastatic cancer cells that are diffusely distributed throughout a treatment site, for example, within an organ. The plurality of light sources are arranged in a spaced-apart array, mounted on a support plate that includes a plurality of conductive traces. A plurality of such arrays are preferably mounted to a flexible sheet that can conform to an outer surface of an organ being treated. Because the light emitted by the light sources is in the IR or near IR waveband, it penetrates deeply into the tissue at the treatment site. The duration of the treatment and the no. of light sources employed for administering the therapy increases the likelihood of two photon absorption by the metastatic cancer cells, which has been shown to activate the photoreactive agent to destroy cancer cells in a tumor, even though the characteristic light absorption waveband of the photoreactive agent is in the UV waveband.

L13 ANSWER 32 OF 44 SCISEARCH COPYRIGHT 2003 ISI (R) DUPLICATE 12
1999:85431 The Genuine Article (R) Number: 157WC. Synthesis of porphyrin nitrogen mustards with potential anti-tumor activities in chemotherapy and **photodynamic therapy**. Chen Z L (Reprint); **Chen J R**; Wan W Q; Xu D Y. CHINESE ACAD SCI, SHANGHAI INST ORGAN CHEM, STATE KEY LAB BIOORGAN & NAT PROD CHEM, 345 LINGLING LU, SHANGHAI 200032, PEOPLES R CHINA (Reprint); MIL MED COLL 2, INST PHARMACEUT CHEM, SHANGHAI 200433, PEOPLES R CHINA. CHINESE JOURNAL OF CHEMISTRY (NOV 1998) Vol. 16, No. 6, pp. 542-548. Publisher: SCIENCE CHINA PRESS, 16 DONGHUANGCHENGGEN NORTH ST, BEIJING 100717, PEOPLES R CHINA. ISSN: 1001-604X. Pub. country: PEOPLES R CHINA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND TALL FORMATS
AB 2,7,12,18-Tetramethyl-13,17-di[3'-N,N-bi(2''-chloroethyl)aminopropyl]porphin and it's 3,8-di(1'-alkyloxyethyl)-analogous of porphyrin-nitrogen mustards were synthesized for the first time. Their structures were determined by spectroscopies and elemental analyses. Most of the compounds possess both the chemotherapeutic and photodynamic effects on tumor and deserve further investigation.

Proceedings of SPIE-The International Society for Optical Engineering, 2972(Optical Methods for Tumor Treatment and Detection: Mechanisms and Techniques in Photodynamic Therapy VI), 161-167 (English) 1997. CODEN: PSISDG. ISSN: 0277-786X. Publisher: SPIE-The International Society for Optical Engineering.

AB The primary focus of laser based oncol. PDT has been on the treatment of skin and hollow organ tumors. Extending PDT to other primary internal lesions and metastasis requires a different approach. Light Sciences has developed a series of semiconductor based devices which will be completely implanted in the patient using established, minimally invasive surgical techniques. These devices are energized noninvasively utilizing inductive coupling. The light delivery system will allow the clinician to modulate the intensity, spatial distribution, and duration of light delivery to maximize the benefits derived from each PDT drug dose. Light Sciences' technol. also enables large tumors to be treated in multiple sessions without time limitations in an outpatient setting. Light Sciences' technol. minimizes patient risk and discomfort, is cost competitive, and expands the treatment options available to the clinician. Avoidance of lengthy operations, bone marrow suppression, and an emphasis on organ preservation allow this next generation of PDT light delivery devices to be effectively integrated with other forms of cancer treatment, if desired. We have termed our technique "Multi-treatment Extended Duration PDT" (MED-PDT). In what follows, I shall describe Light Sciences' technol. and development of minimally invasive oncol. PDT.

L13 ANSWER 34 OF 44 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:51332 Document No.: PREV200200051332. Microminiature illuminator for administering **photodynamic therapy**. **Chen, J. C.**; Swanson, B. D., Bellevue, Wash. USA. ASSIGNEE: LIGHT SCIENCES LIMITED PARTNERSHIP. Patent Info.: US 5571192 Nov. 5, 1996. Official Gazette of the United States Patent and Trademark Office Patents, (Nov. 5, 1996) Vol. 1192, No. 1, pp. 352. ISSN: 0098-1133. Language: English.

L13 ANSWER 35 OF 44 CAPLUS COPYRIGHT 2003 ACS
1993:250800 Document No. 118:250800 Depth of necrosis induced by **photodynamic therapy** with sulfonated aluminum phthalocyanine in S180 fibrosarcoma of mice. Yu, Hongyu; Dong, Rongchun; **Chen, Jiyao**; Cui, Huaixin (Dep. Pathol., 2nd Mil. Med. Univ., Shanghai, 200433, Peop. Rep. China). Proceedings of SPIE-The International Society for Optical Engineering, 1616(International Conference on Photodynamic Therapy and Laser Medicine, 1991), 361-6 (English) 1993. CODEN: PSISDG. ISSN: 0277-786X.

AB In view of explanation of the results that AlSPC-PDT was more effective than HPD-PDT to destroy S180 fibrosarcoma (diam.: 0.5 .apprx. 0.8 cm; thickness: 0.4 .apprx. 0.7 cm) transplanted in white mice, the depth of necrosis of S180 sarcoma in mice in AlSPC-PDT was studied, compared with it in HPD-PDT. Two kinds of HPD were chosen as the control photosensitizers for AlSPC: Photofrin I (P I), Photosensitizing drug-007 (PSD-007). The exptl. tumors in mice were chosen with longitudinal diams. in the range of 0.4 .apprx. 1.0 cm and thickness in the range of 0.7 .apprx. 1.0 cm. A photosensitizer's dose of 10 mg/kg was given (i.p.) for P I-PDT, PSD-007-PDT and AlSPC-PDT. The dose of exposure light (660 .apprx. 750 nm) was 100 J/cm2. The exptl. mice were killed 48 h after PDT to get the tumor necrotic depth. The depth is 0.55 .+-. 0.14 cm (0.30 .apprx. 0.85 cm) in AlSPC-PDT group and 0.35 .+-. 0.12 cm (0.20 .apprx. 0.55 cm) in P I-PDT group and 0.36 .+-. 0.11 cm (0.2) .apprx. 0.50 cm) in PSD-007-PDT group. These differences may be due to the differences of dye's light absorbance spectra that AlSPC's main absorbance peak is at 675

L13 ANSWER 36 OF 44 CAPLUS COPYRIGHT 2003 ACS
1993:250799 Document No. 118:250799 **Photodynamic therapy** in two murine tumor models with sulfonated aluminum phthalocyanine. Yu, Hongyu; Dong, Pengchun; **Chen, Jiyao**; Cai, Huaixin (Dep. Pathol., 2nd Mil. Med. Univ., Shanghai, 200433, Peop. Rep. China). Proceedings of SPIE-The International Society for Optical Engineering, 1616(International Conference on Photodynamic Therapy and Laser Medicine, 1991), 354-60 (English) 1993. CODEN: PSISDG. ISSN: 0277-786X.

AB **Photodynamic therapy** PDT) with sulfonated aluminum phthalocyanine (AlSPC , i.e., AlSPC-PDT, in 2 murine tumor models, is reported herein. Encouraging therapy results were obsd. in S180 fibrosarcoma transplanted in white mice of the Kunming line and in human hepatocellular carcinoma transplanted in balb/c nu/nu nude mice. The exptl. tumors in mice were chosen of 0.8-0.8 cm in diam. and 0.4-0.7 cm in thickness. Photofrin II (PII and photosensitizing drug-007 PSD-007, 2 kinds of porphyrin deriv. dyes, were chosen as the contrast photosensitizers of AlSPC. A dose of 10 mg/kg AlSPC or PII or PSD-007 was given (i.p.). The dose of light (600-750 nm) was 180 J/cm2. "Cure (short-term)" was defined as regression of neoplastic tissue to a nonpalpable tumor within 14 days after PDT. "Cure (long-term)" was defined as absence of local tumor tissue and tumor metastasis on gross and microscopic examns. within 107 days after PDT. The curative results suggest that AlSPC may be a more effective sensitizer than both PII and PSD-007.

L13 ANSWER 37 OF 44 CAPLUS COPYRIGHT 2003 ACS
1993:250798 Document No. 118:250798 Pathologic observation of two kinds of tumors in mice when **photodynamic therapy** with sulfonated aluminum phthalocyanine. Yu, Hongyu; Dong, Pengchun; Min, Hongbo; **Chen, Jiyao**; Cai, Huaixin (Dep. Pathol., 2nd Mil. Med. Univ., Shanghai, 200433, Peop. Rep. China). Proceedings of SPIE-The International Society for Optical Engineering, 1616(International Conference on Photodynamic Therapy and Laser Medicine, 1991), 348-53 (English) 1993. CODEN: PSISDG. ISSN: 0277-786X.

AB The pathol. changes were obsd. in S180 fibrosarcoma transplanted in white mice of Kunming line and in human hepatocellular carcinoma transplanted in balb/c nu/nu nude mice after **photodynamic therapy** (PDT) with sulfonated aluminum phthalocyanine (AlSPC). The exptl. tumors in mice were chosen with diams. in the range of 0.5 .apprx. 0.8 cm. A dose of 10 mg/kg AlSPC was given (i.p.). The dose of light (600 .apprx. 750 nm) was 180 J/cm2. Degeneration of tumor cells, microvascular hyperemia, stroma edema, and hemorrhage were found soon after PDT under the microscope and the hyperemia and hemorrhage in hepatocellular carcinoma seems more obvious than in S180 sarcoma. Heavy hyperemia and hemorrhage can not always be seen in the degenerative and necrotic area in S180 sarcoma. With the transmission electron microscopic technique, the most significant early changes are apparent degeneration of the mitochondria, slight dilation of rough endoplasmic reticula, a small increase of lysosmes, both in tumor cells and in endothelial, collagen fiber degeneration in the subendothelial zone of the capillary wall and in other connective collagen fibers, and slight edema in intercellular space and in the interstitial tissue surrounding capillaries immediately after completion of 30 min PDT. Addnl., the results were discussed, combined with another study of histochem. on 7 kinds of tissue enzymes in hepatocellular carcinoma, which showed the activities of these enzymes reduced from within 30 min to within 6 h after AlSPC-PDT, in which the activity of SDHase was reduced most quickly. The pathol. study suggested a cellular membrane system, esp. mitochondria, was probably one of the

L13 ANSWER 38 OF 44 CAPLUS COPYRIGHT 2003 ACS
1993:250796 Document No. 118:250796 A study on biological effects of sulfonated chloroaluminum phthalocyanine in a transplantable mouse tumor S180). **Chen, Jiyao**; Chen, Wen; Dong, Rongchun; Yu, Hongyu; Cai, Huaixin (Phys. Dep., Fudan Univ., Shanghai, 200433, Peop. Rep. China). Proceedings of SPIE-The International Society for Optical Engineering, 1616(International Conference on Photodynamic Therapy and Laser Medicine, 1991), 319-25 (English) 1993. CODEN: PSISDG. ISSN: 0277-786X.

AB Sulfonated chloroaluminum phthalocyanine (AlClPCS) has been considered as a new photosensitizer with promise for use in **photodynamic therapy** (PDT) of cancer. In this work, biol. effects were studied in mice bearing S180 tumors. It was found in tissue distribution measurements that AlClPCS is selectively accumulated in tumor, the peak tumor concn. of AlClPCS occurs 36 h after administration, with a tumor-to-skin ratio of 3:1. The spectral transmittance measurement in tumor, carried out in vivo at 48 h after administration of AlClPCS at 10 mg/kg, showed that AlClPCS accumulation in tumor affects the light penetration to some extent at its 675 nm main absorption peak, but the transmittance at 675 nm is still comparable to that at 630 nm, the absorption peak of HPD. Temp. measurements in tumors exhibited that the temp. increase is minimal under 100 mW/cm2 irradn. The tumor response to AlClPCS **photodynamic therapy** was encouraging. The cure rate of tumors (20 mice) reached 60% on such condition that the irradn. dose of red light was 180 J/cm2 and the dose of AlClPCS administration was 10 mg/kg, showing AlClPCS has the potential to become a candidate for clin. **photodynamic therapy**.

L13 ANSWER 39 OF 44 CAPLUS COPYRIGHT 2003 ACS
1993:250793 Document No. 118:250793 Mechanism of photodynamic inactivation of hepatocarcinoma cells with sulfonated aluminum phthalocyanine. Yu, Hongyu; Dong, Rongchun; **Chen, Jiyao**; Cai, Huaixin (Dep. Pathol., 2nd Mil. Med. Univ., Shanghai, 200433, Peop. Rep. China). Proceedings of SPIE-The International Society for Optical Engineering, 1616(International Conference on Photodynamic Therapy and Laser Medicine, 1991), 259-65 (English) 1993. CODEN: PSISDG. ISSN: 0277-786X.

AB The mechanism of **photodynamic therapy** (PDT) with sulfonated aluminum phthalocyanine (AlSPC) studied with the human hepatocellular carcinoma cell line in culture herein. Photofrin II (PII) was chosen as the control photosensitizer of AlSPC. Deuterium oxide (D2O), an enhancer of singlet oxygen (1O2), 1,3-diphenylisobenzofuran (DPBF), a quencher of 1O2, glycerol, a quencher of OH radical (OH.bul., superoxide dismutase (SOD), a quencher of O2- radical (O2-.bul.), diethyldithiocarbamate (DDC), an inhibitor of SOD, and glutathione peroxidase, were introduced into both the processes of photodynamic inactivation of human liver cancer cells in culture with AlSPC (AlSPC-PDT) and with PII (PII-PDT). The results suggest that 1O2 is dominantly involved in both PII-PDT and AlSPC-PDT, O2.bul. is involved in AlSPC-PDT to a lower degree than 1O2, while almost not involved in PII-PDT, and OH.bul. is involved in PII-PDT to a lower degree than 1O2, while almost not involved in AlSPC-PDT.

L13 ANSWER 40 OF 44 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 13
93151472 EMBASE Document No.: 1993151472. Studies on pharmacokinetics of sulfonated aluminum phthalocyanine in a transplantable mouse tumor by in vivo fluorescence. **Chen J.-Y.**; Chen W.; Cai H.-X.; Dong R.-C.. Physics Department, Fudan University,Shanghai 200433, China. Journal of Photochemistry and Photobiology B: Biology 18/2-3 (233-237) 1993.

in vivo method. In vivo fluorescence measurements were made on the hind legs of mice, one leg bearing a tumor and the other, without a tumor, being used as a control. These in vivo data were compared with the results obtained from in vitro extraction fluorescence experiments. The results obtained by the two methods showed remarkable agreement, both procedures demonstrating that the concentration of AlPcS in the tumor was substantially higher than that in muscle. In both cases, the maximum tumor to muscle AlPcS concentration ratio occurred at 24-36 h after drug administration. The agreement between the in vivo and in vitro measurements shows that the in vivo fluorescence technique can be used successfully in pharmacokinetic studies of metallo-phthalocyanines in a superficial tumor model. The in vivo technique has the advantages of being rapid and convenient.

L13 ANSWER 41 OF 44 SCISEARCH COPYRIGHT 2003 ISI (R) DUPLICATE 14
92:377994 The Genuine Article (R) Number: HZ415. TIME DETERMINATION OF PHOTOSENSITIZER TISSUE DISTRIBUTION IN MICE BEARING S180 TUMOR SENSITIZED WITH GACL-TETRASULFOPHTHALOCYANINE. **CHEN J Y (Reprint)**; YAO H Y; CHEN W; DONG R C; CAI H X. FUDAN UNIV, DEPT NUCL SCI, DEPT PHYS, SHANGHAI 200433, PEOPLES R CHINA (Reprint); MIL MED COLL 2, DEPT PATHOL ANAT, SHANGHAI, PEOPLES R CHINA. INTERNATIONAL JOURNAL OF RADIATION BIOLOGY (JUN 1992) Vol. 61, No. 6, pp. 773-776. ISSN: 0020-7616. Pub. country: PEOPLES REPUBLIC OF CHINA. Language: ENGLISH.

L13 ANSWER 42 OF 44 MEDLINE DUPLICATE 15
92119548 Document Number: 92119548. PubMed ID: 1837493. Studies on the photochemical and photocytotoxic properties of the new EDT photosensitizer aluminum sulfonated phthalocyanine. **Chen J Y**; Xie R; Chen S M; Lu F D; Chen K T; Cai H X. (Department of Physics, Fudan University, Shanghai, P.R. China.) CANCER BIOCHEMISTRY BIOPHYSICS, (1991 Aug) 12 (2) 103-16. Journal code: 7904514. ISSN: 0309-7233. Pub. country: ENGLAND: United Kingdom. Language: English.

AB The properties of photosensitization of sulfonated aluminum phthalocyanine (ALSPC), a new photosensitizer of potential use in cancer **photodynamic therapy** (PDT) was studied on both the molecular and cellular levels. The mechanism of ALSPC photosensitization on the molecular level was investigated by testing its efficiency of singlet oxygen ($^1O_2$) production, using the method of tryptophan degradation and that of ESR spectroscopy and observing the enhancing effect of D_2O and the quenching effect of NaN_3. Results of all these experiments confirmed the important role of the Type II or $^1O_2$ mechanism in ALSPC photosensitization. In our in-vitro experiments, ALSPC's incorporation into cells and its photocytotoxic effect were investigated on a human liver cancer cell line. The cell incorporation was illustrated by the laser-excited fluorescence spectra emitted both from cell homogenate and cell monolayers incubated with ALSPC aqueous solution. The position of fluorescence peak observed, implied that ALSPC exists in the cells mainly as monomers. The efficiency of cell killing of ALSPC photosensitization was estimated by counting surviving cells with the method of trypan blue staining and by the method of radioisotope labelling. Experiments using the latter method also showed DNA damage caused by ALSPC photosensitization.

L13 ANSWER 43 OF 44 CAPLUS COPYRIGHT 2003 ACS
1991:602111 Document No. 115:202111 Experimental study of the photokilling effect of a new photosensitizer, aluminum phthalocyanine, on human hepatoma cell line. Lu, Fudu; Zhan, Rongzhou; Mao, Hongjie; Chen, Junhen; **Chen, Jiyao**; Cai, Huaixin (Dep. Pathoanat., 2nd Mil. Med. Coll.,

vitro. ALSPC was not cytotoxic even at 100 .mu.g/mL. In photosensitizing expts. with different irradn. wavebands, the red waveband had the most marked killing effect, which coincided with the peak absorption band of ALSPC. As the best penetration waveband for human body tissues is located in this red region, ALSPC has a potential value in clin. application. The photosensitizing inactivation of cells was also estd. by [3H]TDR radioisotope labeling method, confirming that ALSPC had photokilling ability. ALSPC had almost the same photokilling activity on cancer cells as HPD.

L13 ANSWER 44 OF 44 CAPLUS COPYRIGHT 2003 ACS
1991:224634 Document No. 114:224634 A comparative study on photosensitization by aluminum sulfonated phthalocyanine and hematoporphyrin derivatives. **Chen, Jiyao**; Chen, Shiming; Chen, Haitai; Cai, Huaixin (Phys. Dep., Fudan Univ., Shanghai, Peop. Rep. China). Shengwu Huaxue Yu Shengwu Wuli Xuebao, 22(5), 477-82 (Chinese) 1990. CODEN: SHWPAU. ISSN: 0582-9879.

AB Photosensitization by Al sulfonated phthalocyanine (ALSPC) was studied and compared with that of the photosensitizer HPD, which is widely used at present in the **photodynamic therapy** (PDT) of cancer. Results from in vitro cellular expts. showed that, when irradiated with red light, the photodamaging effect on human cancer cells by both photosensitizers (using the same sensitizer concn.), is enhanced with an increase in irradn. dose and with an increase in time of incubation of cells in sensitizer solns. At longer incubation times, their photodamage efficiency were close to each other. When exposed to room light, the damaging effect of ALSPC is weaker than that of HPD, showing a lower light-induced detrimental side effect, which is desirable when used in PDT. ESR expts. on a submol. level showed that singlet O (1O2) is an intermediate product in the photosensitization reaction of both these photosensitizers. Under red light irradn. with the same doses, the yield of 1O2 in ALSPC photosensitization is higher than that of HPD, chiefly due to ALSPC's higher absorbance of red light, but its quantum yield is lower than that of HPD.

=> s antibody
L14 2397687 ANTIBODY

=> s l14 and VEGF receptor
L15 1033 L14 AND VEGF RECEPTOR

=> s l15 and conjugate
L16 14 L15 AND CONJUGATE

=> dup remove l16
PROCESSING COMPLETED FOR L16
L17 11 DUP REMOVE L16 (3 DUPLICATES REMOVED)

=> d l17 1-11 bib abs

L17 ANSWER 1 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:457604 Document No.: PREV200200457604. **Antibody conjugate** kits for selectively inhibiting VEGF. Thorpe, Philip E.; Brekken, Rolf A.. ASSIGNEE: Board of Regents, The University of Texas System, Austin, TX, USA. Patent Info.: US 6416758 July 09, 2002. Official Gazette of the United States Patent and Trademark Office Patents, (July 9, 2002) Vol. 1260, No. 2, pp. No Pagination. http://www.uspto.gov/web/menu/p

regression, and yet have improved safety due to their specificity. The present invention thus provides new **antibody**-based compositions, methods and combined protocols for treating cancer and other angiogenic diseases. Advantageous immunoconjugate and prodrug compositions.

L17 ANSWER 2 OF 11 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
2002:170997 Document No.: PREV200200170997. **Antibody** **conjugate** compositions for selectively inhibiting VEGF. Thorpe, Philip E.; Brekken, Rolf A.. ASSIGNEE: Board of Regents, The University of Texas System. Patent Info.: US 6342221 January 29, 2002. Official Gazette of the United States Patent and Trademark Office Patents, (Jan. 29, 2002) Vol. 1254, No. 5, pp. No Pagination. http://www.uspto.gov/web/menu/patdata.html. e-file. ISSN: 0098-1133. Language: English.

AB Disclosed are **antibodies** that specifically inhibit VEGF binding to only one (VEGFR2) of the two **VEGF receptors**. The **antibodies** effectively inhibit angiogenesis and induce tumor regression, and yet have improved safety due to their specificity. The present invention thus provides new **antibody**-based compositions, methods and combined protocols for treating cancer and other angiogenic diseases. Advantageous immunoconjugate and prodrug compositions and methods using the new VEGF-specific **antibodies** are also provided.

L17 ANSWER 3 OF 11 CAPLUS COPYRIGHT 2003 ACS
2002:475777 Document No. 137:233014 Ascorbic acid analogs for metalloradiopharmaceuticals. Liu, Shuang (Bristol-Myers Squibb Pharma Company, USA). PCT Int. Appl. WO 2002067859 A2 20020906, 81 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US5199 20020222. PRIORITY: US 2001-PV271389 20010226.

AB The invention relates to the use of ascorbic acid analogs as buffering reagents and chelating agents for the prepn. of metalloradiopharmaceuticals. Also, the invention relates to the use of ascorbic acid as a buffering reagent, a chelating agent, and a stabilizer for the prepn. and stabilization of radiopharmaceuticals and processes for making and using the same. Examples are provided of 90Y, 111In, and 177Lu radiopharmaceuticals prepd. from the ligands and chlorides of the radionuclides using ascorbic acid as the buffer agent, transfer ligand and radiolytic stabilizer.

L17 ANSWER 4 OF 11 SCISEARCH COPYRIGHT 2003 ISI (R)
2002:[illegible] The Genuine Article (R) Number: [illegible]. Gene therapy of murine solid tumors with T cells transduced with a retroviral vascular endothelial growth factor-immunotoxin target gene. Jin N; Chen W; Blazar B R; Ramakrishnan S; Vallera D A (Reprint). Univ Minnesota, Ctr Canc, Dept Therapeut Radiol Radiat Oncol, Sect Expt Canc Immunol, Mayo Mail Code 367, Harvard St S E River Rd, Minneapolis, MN 55455 USA (Reprint); Univ Minnesota, Ctr Canc, Dept Therapeut Radiol Radiat Oncol, Sect Expt Canc Immunol, Minneapolis, MN 55455 USA; Univ Minnesota, Ctr Canc, Dept Pediat, Minneapolis, MN 55455 USA; Univ Minnesota, Ctr Canc, Dept Pharmacol, Minneapolis, MN 55455 USA. HUMAN GENE THERAPY (MAR 2002) Vol. 13, No. 4,

AB Solid tumor growth can be inhibited by targeting its neovasculature with vascular endothelial growth factor (VEGF)-toxin fusion proteins FPs), but these agents have been limited by their inability to localize at the tumor site. In this study, we devised a gene therapy approach intended to deliver VEGF-toxin directly to tumor. Antigen-specific cytotoxic T lymphocytes CTLs) served as vehicles to deliver a retroviral VEGF-toxin fusion protein to its specific leukemia cell target in vivo. A retroviral vector was constructed for gene therapy with VEGF positioned downstream of its 27-amino acid leader sequence, which promoted secretion of a catalytic immunotoxin containing either truncated diphtheria toxin or Pseudomonas exotoxin A. VEGF was chosen on the basis of the expression of **VEGF receptor** on endothelial cells in the tumor neovasculature. The VEGF FP was first expressed and secreted by mammalian NIH 3T3 cells. Intracellular expression of both VEGF and toxin was verified by immunofluorescence. In vitro, supernatants collected from transfected cells specifically inhibited the growth of **VEGF receptor**-expressing human umbilical vein endothelial cells (HUVECs), but not a control cell line. In vivo findings correlated with in vitro findings. A retroviral vector containing the target gene and a nerve growth factor receptor (NGFR) reporter gene was used to transiently transduce T15, a CD8(+) CTL line that specifically recognizes C1498, a lethal C57BL/6 myeloid tumor. Transduced T15 cells injected intravenously significantly inhibited the growth of subcutaneous tumor, whereas non-transduced controls did not. Together, these data indicate that gene therapy of T cells with retrovirus containing a VEGF-immunotoxin target gene may be a valid means of inhibiting a broad range of solid tumors dependent on angiogenesis.

L17 ANSWER 5 OF 11 CAPLUS COPYRIGHT 2006 ACS
2002:272281 Document No. 137:37584 Molecular Vehicles for Targeted Drug Delivery. Backer, Marina V.; Aloise, Renee; Przekop, Kristen; Stoletov, Konstantin; Backer, Joseph M. (SibTech Inc., Newington, CT, 06111, USA). Bioconjugate Chemistry, 13(3), 462-467 (English) 2002. CODEN: BCCHES. ISSN: 1043-1802. Publisher: American Chemical Society.
AB Targeted drug delivery by cell-specific cytokines and **antibodies** promises greater drug efficacy and reduced side effects. We describe a novel strategy for assembly of drug delivery vehicles that does not require chem. modification of targeting proteins. The strategy relies on a noncovalent binding of standardized "payload" modules to targeting proteins expressed with a "docking" tag. The payload modules are constructed by linking drug carriers to an adapter protein capable of binding to a docking tag. Using fragments of bovine RNase A as an adapter protein and a docking tag, we have constructed vascular endothelial growth factor (VEGF) based vehicles for gene delivery and for liposome delivery. Assembled vehicles displayed remarkable selectivity in drug delivery to cells overexpressing **VEGF receptors**. We expect that our strategy can be employed for targeted delivery of many therapeutic or imaging agents by different recombinant targeting proteins.

L17 ANSWER 6 OF ... SCISEARCH COPYRIGHT 2006 ISI (R)
2002:756902 The Genuine Article (R) Number: 606QF. Tumor-targeting properties of **antibody**-vascular endothelial growth factor fusion proteins. Halin C; Niesner U; Villani M E; Zardi L; Neri D (Reprint). Swiss Fed Inst Technol, Inst Pharmaceut Sci, Bldg 36 M14, Winterthurerstr 190, CH-8057 Zurich, Switzerland (Reprint); Swiss Fed Inst Technol, Inst Pharmaceut Sci, CH-8057 Zurich, Switzerland; Natl Inst Canc Res, Lab Cell Biol, Genoa, Italy. INTERNATIONAL JOURNAL OF CANCER (10 NOV 2002) Vol. 102, No. 2, pp. 109-116. Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC, 605

is the poor penetration of **antibodies** into tumor tissue. Vasoactive immunoconjugates have been proposed as a means of increasing **antibody** uptake in tumors. In principle, VEGF (also known as vascular permeability factor) could selectively alter vascular permeability, leading to improved tumor targeting. A possible role for VEGF in the targeting of tumor neovasculature has been postulated, based on the overexpression of **VEGF receptors** in tumor endothelial cells. However, quantitative bio-distribution studies on this topic are not available. In this report, we describe the cloning, expression, characterization and bio-distribution in tumor-bearing mice of **antibodies** fused to either VEGF(120) or VEGF(164) The MAb fragments chosen for analysis were scFv(L19), specific for the ED-B domain of fibronectin, a marker of angiogenesis, and scFv(HyHEL-10), a negative control **antibody** of irrelevant specificity in mice. Neither unconjugated VEGF nor scFv(HyHEL-10)-VEGF fusion proteins showed accumulation in the tumor (tumor:blood ratios approx. 1 at 4 hr and 24 hr postinjection). By contrast, scFv(L19)-VEGF(120) but not scFv(L19)-VEGF(164) showed significant accumulation in tumors (tumor:blood ratio = 9.3 at 24 hr) but was not superior to unconjugated scFv(L19). Preinjection of unlabeled scFv(L19)-VEGF(120) prior to administration of radiolabeled fusion protein led to increased accumulation of radiolabeled scFv(L19)-VEGF(120) in the tumor but only at very high concentrations (20 mg/mouse). (C) 2002 Wiley-Liss, Inc.

L17 ANSWER 7 OF 11 CAPLUS COPYRIGHT 2003 ACS
2001:545508 Document No. 135:132464 Cyclic peptide inhibitors of VEGF, VEGF-C, and VEGF-D, preparation methods, pharmaceutical compositions, and therapeutic use. Achen, Marc G.; Hughes, Richard A.; Stacker, Steven; Cendron, Angela (Ludwig Institute for Cancer Research, USA). PCT Int. Appl. WO 2001052875 A1 20010726, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US1533 20010118. PRIORITY: US 2000-PV176293 20000118; US 2000-PV204590 20000516.

AB The invention provides monomeric monocyclic peptide inhibitors and dimeric bicyclic peptide inhibitors based on exposed loop fragments of a growth factor protein, e.g. loop 1, loop 2 or loop 3 of VEGF-D, as well as methods of making them, pharmaceutical compns. contg. them, and therapeutic methods of use.

L17 ANSWER 8 OF 11 CAPLUS COPYRIGHT 2003 ACS
2001:64704 Document No. 135:205162 Single-chain **antibodies** recognizing the human vascular endothelial growth factor receptor-2 (VEGFR-2/KDR). Boeldicke, Thomas; Welch, Herbert; Tesar, Michael; Yayon, Avner (Gesellschaft fuer Biotechnologische Forschung m.b.H. (GBF), Germany). Eur. Pat. Appl. EP 1113 032 A1 20010705, 35 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO. (English). CODEN: EPXXDW. APPLICATION: EP 2000-104082 20000223.

AB The invention relates to specific single-chain **antibodies** (scFv's) recognizing the human vascular endothelial growth factor receptor-2 (VEGFR-2/KDR) which show no cross reactivity to the human **VEGF-receptor** 1 (VEGFR-1). The scFv's have clin.

L17 ANSWER 9 OF 11 MEDLINE DUPLICATE 1
2001177066 Document Number: 21039018. PubMed ID: 11196310. Generation and characterization of recombinant vascular targeting agents from hybridoma cell lines. Gottstein C; Wels W; Ober B; Thorpe P E. (University of Texas Southwestern Medical Center, Dallas, TX, USA.. claudia.gottstein@uni-koeln.de) . BIOTECHNIQUES, (2001 Jan) 30 (1) 190-4, 196, 198 passim. Journal code: 8306785. ISSN: 0736-6205. Pub. country: United States. Language: English.

AB Vascular targeting agents (VTAs) can be produced by linking **antibodies** or **antibody** fragments directed against endothelial cell markers to effector moieties. So far, it has been necessary to produce the components of VTAs (**antibody**, **antibody** fragment, linker, and effector) separately and, subsequently, to **conjugate** them by biochemical reactions. We devised a cloning and expression system to allow rapid generation of recombinant VTAs from hybridoma cell lines. The VTAs consist of a single chain Fv **antibody** fragment as a targeting moiety and either truncated Pseudomonas exotoxin (resulting in immunotoxins) or truncated human tissue factor (resulting in coaguligands) as effectors. The system was applied to generate recombinant immunotoxins and coaguligands directed against endoglin, vascular endothelial growth factor (VEGF):**VEGF receptor** (VEGFR) complex and vascular cell adhesion molecule 1 (VCAM-1). The fusion proteins exhibited similar functional activity to analogous biochemical constructs. This is the first report to describe the generation and characterization of recombinant coaguligands.

L17 ANSWER 10 OF 11 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
2001278994 EMBASE VEGF-**VEGF receptor** complexes as markers of tumor vascular endothelium. Brekken R.A.; Thorpe P.E.. P.E. Thorpe, Univ. of TX Southwestern Med. Ctr., Department of Pharmacology, Simmons Cancer Center, 6000 Harry Hines Blvd., Dallas, TX 75390-9111, United States. philip.thorpe@utsouthwestern.edu. Journal of Controlled Release 74/1-3 (173-181) 6 Jul 2001.
Refs: 44.
ISSN: 0168-3659. CODEN: JCREEC.
Publisher Ident.: S 0168-3659(01)00333-9. Pub. Country: Netherlands.
Language: English. Summary Language: English.

AB Vascular endothelial growth factor (VEGF) is a primary stimulant of the vascularization of solid tumors and has therefore been the focus of intense research aimed at blocking its activity in solid tumors. VEGF production by tumor cells is induced by oncogenic gene mutations and hypoxic conditions inside the tumor mass. **VEGF receptor** expression on endothelial cells lining blood vessels in the tumor is also induced by hypoxia and the increased local concentration of VEGF. Therefore in the tumor microenvironment there is an upregulation of both VEGF and its receptor leading to a high concentration of occupied receptor on tumor vascular endothelium. The VEGF-**VEGF receptor** complex (VEGF-VEGFR) presents an attractive target for the specific delivery of drugs or other effectors to tumor endothelium. Herein we review the development of monoclonal **antibodies** that selectively bind to the VEGF-VEGFR and their use as targeting agents that selectively bind to VEGF activated blood vessels. Additionally, we summarize the properties of 2C3, a novel monoclonal anti-VEGF **antibody** that blocks VEGF from binding to VEGFR2 but not VEGFR1. 2C3 may be utilized as both an anti-angiogenic agent by inhibiting VEGFR2 activity and potentially as a vascular targeting agent by binding to blood vessels that express the VEGF-VEGFR1 complex. .COPYRGT. 2001 Elsevier Science B.V. All

Agus, David B.; Scheinberg, David; Roberts, Wendy; Zelenetz, Andrew D. (Sloan-Kettering Institute for Cancer Research, USA . PCT Int. Appl. WO 9957981 A1 19991118, 43 pp. DESIGNATED STATES: W: CA, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English . CODEN: PIXXD2. APPLICATION: WO 1999-US10065 19990507. PRIORITY: US 1998-84874 19980508.

AB The authors disclose treatment of non-Hodgkin's lymphoma (NHL) by the administration of CD20 itself, or an immunogenic fragment of the extracellular domain, coupled to or administered with an antigenic carrier moiety such as keyhole limpet hemocyanin (KLH). This results in the stimulation of the prodn. of polyclonal **antibodies** against CD20 (or an immunogenic fragment thereof) which has the effect of reducing the no. of B-cells, including malignant B-cells. A similar approach may be used for therapy of other diseases and conditions in which target cells possess a transmembrane protein. This would include, for example, Her2/neu, **VEGF receptor**, epidermal growth factor receptor, the CD19 mol., interleukin-2-receptor, interleukin-4-receptor, and the P-glycoprotein, also known as the multidrug-resistance protein.

=> s l15 and VEGFR
L19 281 L15 AND VEGFR

=> s l19 and macular degeneration
L19 1 L19 AND MACULAR DEGENERATION

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L19 ANSWER 1 OF 1 MEDLINE
1999364929 Document Number: 99364929. PubMed ID: 10433935. Polarized vascular endothelial growth factor secretion by human retinal pigment epithelium and localization of vascular endothelial growth factor receptors on the inner choriocapillaris. Evidence for a trophic paracrine relation. Blaauwgeers H G; Holtkamp G M; Rutten H; Witmer A N; Koolwijk P; Partanen T A; Alitalo K; Kroon M E; Kijlstra A; van Hinsbergh V W; Schlingemann R O. (Department of Ophthalmology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands.) AMERICAN JOURNAL OF PATHOLOGY, (1999 Aug) 155 (2) 421-8. Journal code: 0370502. ISSN: 0002-9440. Pub. country: United States. Language: English.

AB The retinal pigment epithelium (RPE) maintains the choriocapillaris (CC) in the normal eye and is involved in the pathogenesis of choroidal neovascularization in age-related **macular degeneration**. Vascular endothelial growth factor-A (VEGF) is produced by differentiated human RPE cells in vitro and in vivo and may be involved in paracrine signaling between the RPE and the CC. We investigated whether there is a polarized secretion of VEGF by RPE cells in vitro. Also, the localization of **VEGF receptors** in the human retina was investigated. We observed that highly differentiated human RPE cells, cultured on transwell filters in normoxic conditions, produced two- to sevenfold more VEGF toward their basolateral side as compared to the apical side. In hypoxic conditions, VEGF-A secretion increased to the basal side only, resulting in a three- to 11-fold higher basolateral secretion. By immunohistochemistry in 30 human eyes and in two cynomolgus monkey eyes, KDR (**VEGFR**-2) and flt-4 (**VEGFR**-3) were preferentially localized at the side of the CC endothelium facing the RPE cell layer, whereas flt-1 (**VEGFR**-1) was found on the inner CC and on other choroidal vessels. Our results indicate that RPE secretes VEGF toward its basal side where its receptor KDR is located on the

normal eye functioning. Up-regulated basolateral VEGF secretion by RPE in hypoxia or loss of polarity of VEGF production may play a role in the pathogenesis of choroidal neovascularization.

=> s l18 and eye
L20 14 L18 AND EYE

=> s l20 and photodynamic therapy
L21 4 L20 AND PHOTODYNAMIC THERAPY

=> s l19 and photodynamic therapy
L22 0 L19 AND PHOTODYNAMIC THERAPY

=> s photodynamic therapy
L23 3834 PHOTODYNAMIC THERAPY

=> s l23 and chlorin
L24 1583 L23 AND CHLORIN

=> s l24 and targeting
L25 83 L24 AND TARGETING

=> s l25 and antibody
L26 25 L25 AND ANTIBODY

=> dup remove l26
PROCESSING COMPLETED FOR L26
L27 19 DUP REMOVE L26 (6 DUPLICATES REMOVED)

=> d l27 1-19 cbib abs

L27 ANSWER 1 OF 19 CAPLUS COPYRIGHT 2003 ACS
2002:964122 Document No. 138:21428 Photoimmunotherapies for cancer using photosensitizer immunoconjugates and combination therapies. Hasan, Tayyaba; Savellano, Mark D.; Skobe, Mihaela (The General Hospital Corporation, USA). PCT Int. Appl. WO 2002100326 A2 20021219, 123 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US13776 20020501. PRIORITY: US 2001-PV287767 P 20010501; US 2001-PV338961 P 20011207.

AB The present invention relates to photosensitizer immunoconjugate compns. and combination therapies for use in cancer related photodynamic treatments and diagnostic methods. Photosensitizer immunoconjugates comprising a photosensitizer conjugated to a tumor-specific and/or tumoricidal **antibody** and processes for the prepn. thereof are described. The use of photosensitizer immunoconjugates (PICs) offers improved photosensitizer delivery specificity for diagnostic and therapeutic applications. In examples provided, prepn. of PEGylated verteporfin (BPD-MA -**antibody** conjugates is described and results on its cellular uptake, subcellular localization, photochem. properties and cytotoxic photodynamic action presented. The antitumor

367-384. ISSN: 0015-5632. Pub. country: CZECH REPUBLIC. Language: ENGLISH. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Drug **targeting** is an attractive new approach to killing cancer cells while leaving normal tissue unharmed. Recently we have developed a new generation of **antibody**-targeted immunosuppressive (cyclosporin A) and cytostatic (daunomycin, doxorubicin) drugs and photosensitizers (**chlorin** e(6)) effective in vitro and in vivo. The drugs and the **targeting antibody** (polyclonal and monoclonal) are conjugated to the oligopeptidic side chains of a water-soluble synthetic carrier, copolymer of N-(2-hydroxypropyl)methacrylamide. The composition of the side chains ensures the stability of the linkage between the drug and the polymeric carrier in the bloodstream and its intralysosomal degradability which is a prerequisite for the pharmacological activity of the preparation. **Antibody**-targeted polymer bound drugs show considerably decreased hepatotoxicity, cardiotoxicity, myelotoxicity and nephrotoxicity. Two adriamycin-HPMA copolymers are in Phase I/II clinical trials in United Kingdom.

L27 ANSWER 13 OF 19 MEDLINE DUPLICATE 2

95365438 Document Number: 95365438. PubMed ID: 7638262. **Targeting** activated lymphocytes with **photodynamic therapy**: susceptibility of mitogen-stimulated splenic lymphocytes to benzoporphyrin derivative (BPD) photosensitization. Obochi M O; Canaan A J; Jain A K; Richter A M; Levy J G. (Department of Microbiology and Immunology, University of British Columbia, Vancouver, Canada.) PHOTOCHEMISTRY AND PHOTOBIOLOGY, (1995 Jul) 62 (1) 169-75. Journal code: 0376425. ISSN: 0031-8655. Pub. country: United States. Language: English.

AB Benzoporphyrin derivative monoacid ring A (BPD), a hydrophobic **chlorin**-like porphyrin derivative, which fluoresces strongly at 690 nm, may have potential for both oncologic and nononcologic applications in **photodynamic therapy** (PDT). To study the influence of cellular characteristics on the uptake of BPD, the murine tumor cell line (P815), and in vitro and in vivo concanavalin A (Con A) -stimulated and unstimulated murine splenic lymphocytes were incubated with 1 micrograms/mL BPD at 37 degrees C for 0-60 min. At various times, cells were lysed and the amount of BPD taken up by cells was quantified by fluorescence measurements. The subsets of cells taking up BPD were analyzed using a panel of monoclonal **antibodies** and the Coulter XL fluorescence-activated cell sorter. Furthermore, Con A-stimulated and unstimulated spleen cells were incubated with 0-50 ng/milter of BPD for 1 h prior to exposure to red light (7.2 J/cm2). Cell survival 24 h post-PDT was measured by the MTT assay. We found that the rapidly dividing tumor cell line and mitogen-stimulated murine T cells (mainly CD4+/IL-2R+) took up significantly more BPD (5-10-fold) than do unstimulated splenic lymphocytes. Increased BPD uptake correlated with greater photoinactivation when these cells were exposed to light at a wavelength of 690 nm. These findings suggest that activated cells of the immune system may be a target for photoinactivation by BPD.

L27 ANSWER 14 OF 19 SCISEARCH COPYRIGHT 2005 ISI (R)

94:21669 The Genuine Article (R) Number: NE024. APPROACHES TO TARGETED PHOTODYNAMIC TUMOR-THERAPY. KLYASHCHITSKY B A (Reprint); NECHAEVA I S; PONOMARYOV G V. RUSSIAN ACAD MED SCI, INST BIOMED CHEM, POGODINSKAYA STR 10, MOSCOW 119832, RUSSIA (Reprint); MINIST HLTH, INST BIOPHYS, MOSCOW 123182, RUSSIA. JOURNAL OF CONTROLLED RELEASE (FEB 1994) Vol. 29, No. 1-2, pp. 1-16. ISSN: 0168-3659. Pub. country: RUSSIA. Language: ENGLISH. *ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS*

AB Photodynamic therapy

compartment into the cytosol, the affinity of the carrier to the drug and the concentration of the carrier. Targeted chemotherapy is also significantly influenced by the antigenic modulation and/or immunoselection of tumor cells. The binding of drug (toxin) to targetable polymeric carrier considerably decreases unwanted side toxicity. (C) 1998 Elsevier Science B.V.

L10 ANSWER 7 OF 12 CAPLUS COPYRIGHT 2003 ACS
1995:474781 Document No. 123:266107 Pretargeting methods and compounds for pretargeted delivery of diagnostic and therapeutic agents. Theodore, Louis J.; Meyer, Damon L.; Mallett, Robert W.; Kasina, Sudhakar; Reno, John M.; Axworthy, Donald B.; Gustavson, Linda M. (Neorx Corp., USA). PCT Int. Appl. WO 9515979 A1 19950615, 290 pp. DESIGNATED STATES: W: CA, JP; RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 1994-US14174 19941207. PRIORITY: US 1993-163186 19931207.

AB Methods, compds., compns. and kits that relate to pretargeted delivery of diagnostic and therapeutic agents are disclosed. Examples include e.g. in vivo anal. of a radiolabeled chelate-biotin conjugate administered after **antibody** pretargeting, clearing agent evaluation, two- and three-step pretargeting methods., and prepn. of conjugates. The methods may also be used to increase photosensitizing agent localization.

L10 ANSWER 8 OF 12 CAPLUS COPYRIGHT 2003 ACS
1995:794487 Document No. 123:106714 **Targeting** activated lymphocytes with photodynamic therapy: susceptibility of mitogen-stimulated splenic lymphocytes to benzoporphyrin derivative (BPD) photosensitization. Obochi, Modestus O. K.; Canaan, Alice J.; Jain, Ashok K.; Richter, Anna M.; Levy, Julia G. (Dep. Microbiology and Immunology, Univ. British Columbia, Vancouver, BC, V6T 1Z3, Can.). Photochemistry and Photobiology, 62(1), 169-75 (English) 1995. CODEN: PHCBAP. ISSN: 0031-8655. Publisher: American Society for Photobiology.

AB Benzoporphyrin deriv. monoacid ring A (BPD), a hydrophobic **chlorin**-like porphyrin deriv., which fluoresces strongly at 690 nm, may have potential for both oncol. and nononcol. applications in photodynamic therapy (PDT). To study the influence of cellular characteristics on the uptake of BPD, the murine tumor cell line (P815), and in vitro and in vivo Con A-stimulated and unstimulated murine splenic lymphocytes were incubated with 1 .mu.g/mL BPD at 37.degree. for 0-60 min. At various times, cells were lysed and the amt. of BPD taken up by the cells was quantified by fluorescence measurements. The subsets of cells taking up BPD were analyzed using a panel of monoclonal **antibodies** and the Coulter XL fluorescence-activated cell sorter. Furthermore, Con A-stimulated and unstimulated spleen cells were incubated with 0-50 ng/mL of BPD for 1 h prior to exposure to red light (7.2 J/cm2). Cell survival 24 h post-PDT was measured by the MTT assay. We found that the rapidly dividing tumor cell line and mitogen-stimulated T cells (mainly CD4+ IL-2R+) took up significantly more BPD (5-10-fold) than do unstimulated splenic lymphocytes. Increased BPD uptake correlated with greater photoinactivation when these cells were exposed to light at a wavelength of 647 nm. These findings suggest that activated cells of the immune system may be a target for photoinactivation by BPD.

L10 ANSWER 9 OF 12 SCISEARCH COPYRIGHT 2003 ISI (R)
94:216303 The Genuine Article (R) Number: NE024. APPROACHES TO TARGETED PHOTODYNAMIC TUMOR-THERAPY. KLYASHCHITSKY B A (Reprint); NECHAEVA I S; PONOMAREV G V. RUSSIAN ACAD MED SCI, INST BIOMED CHEM, POGODINSKAYA STR

conjugates but not for free chlorine6. Cationic species had a high uptake in the lungs compared to anionic species. The photoimmunoconjugates show an advantage over literature reports of other photosensitizers, which can result in tumour:normal liver ratios of less than 1.

L27 ANSWER 8 OF 19 SCISEARCH COPYRIGHT 2003 ISI (R)
1998:919048 The Genuine Article (R) Number: 143YF. Photocytotoxic action of EGF-PVA-Sn(IV)**chlorin** e(6) and EGF-dextran-Sn(IV)**chlorin** e(6) internalizable conjugates on A431 cells. Gijsens A; deWitte P (Reprint). KATHOLIEKE UNIV LEUVEN, FAC FARMACEUT WETENSCHAPPEN, LAB FARMACEUT BIOL FYTOFARMACOL, VAN EVENSTR 4, B-3000 LOUVAIN, BELGIUM (Reprint); KATHOLIEKE UNIV LEUVEN, FAC FARMACEUT WETENSCHAPPEN, LAB FARMACEUT BIOL FYTOFARMACOL, B-3000 LOUVAIN, BELGIUM. INTERNATIONAL JOURNAL OF ONCOLOGY (DEC 1998) Vol. 13, No. 6, pp. 1171-1177. Publisher: INT JOURNAL ONCOLOGY, C/O PROFESSOR D A SPANDIDOS, EDITORIAL OFFICE, 1, S MERKOURI ST, ATHENS 116 35, GREECE. ISSN: 1019-6439. Pub. country: GREECE. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Certain tumour cells, such as squamous carcinoma cells, express an increased number of epidermal growth factor (EGF) receptors. The goal of this study was the targeted delivery of Sn(IV)**chlorin** e(6) (SnCe6) to tumours that overexpress the EGF receptor. Therefore EGF was conjugated to the photosensitizer through a carrier, such as dextran (Dex) and polyvinylalcohol (PVA). These conjugates were then compared to a conjugate of the photosensitizer to dextran or PVA alone. The EGF-Dex-SnCe6 conjugates bound specifically to the EGF receptors of the human squamous carcinoma cell line A431 in contrast to EGF-PVA-SnCe6. However, EGF-PVA-SnCe6 exhibited a higher photocytotoxicity (CC50, 2.8 mu M) than EGF-Dex-SnCe6 (CC50, >10 mu M) and SnCe6 (CC50, >10 mu M). PVA-SnCe6 had a similar photocytotoxicity (CC50, 3.5 mu M) to EGF-PVA-SnCe6, indicating that PVA, more than EGF, plays a determinant role in the uptake of the conjugates by A431 cells. Together with the improved affinity of EGF-Dex-SnCe6 over EGF-PVA-SnCe6 for the EGF receptor, the former displayed a small increased photocytotoxicity over Dex-SnCe6, reflecting a limited EGF receptor mediated uptake effect. It was concluded that the photodynamic activity of the EGF-conjugate turns out to be strongly dependent on the carrier used.

L27 ANSWER 9 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
1998066753 EMBASE HPMA copolymer-anticancer drug-OV-TL16 **antibody** conjugates. II. Processing in epithelial ovarian carcinoma cells in vitro. Omelyanenko V.; Gentry C.; Kopeckova P.; Kopecek J., J. Kopecek, Dept. Pharm./Pharmaceut. Chemistry, University of Utah, Salt Lake City, UT 84112-9450, United States. jindrich.kopecek@m.cc.utah.edu. International Journal of Cancer 75/4 (600-608) 9 Feb 1998.
Refs: 24.
ISSN: 0020-7136. CODEN: IJCNAW. Pub. Country: United States. Language: English. Summary Language: English.

AB The binding, internalization, subcellular trafficking and in vitro cytotoxicity of N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer-anticancer drug-OV-TL16 **antibody** (Ab) conjugates in the ovarian carcinoma OVCAR-3 cell line have been investigated. Adriamycin (ADR) and mesochlorin e6 mono(N-2-aminoethylamide) (Mce6) photosensitizer were used as anti-cancer drugs. Targeted (Ab-containing) conjugates were compared with non-targeted HPMA copolymerdrug conjugates and with free drugs. Targeted conjugates were taken up rapidly by cells and detected within lysosomes by confocal fluorescence microscopy. The ADR attached to

no fluorescence could be detected in the cell nuclei. Binding the drugs to a non-targeted HPMA copolymer decreased their cytotoxicity in vitro. The IC50 dose increased from 2 M for free ADR to 150 M for P(GFLG)-ADR (P is the HPMA copolymer backbone) and from 0.34 .mu.M for free Mce6 (with light) to 190 .mu.M for P-(GG)-Mce6. However, attachment of OV-TLI 6 Abs rendered HPMA copolymer-drug conjugates bioreccgnizable by OVCAR-3 cells and markedly increased their cytotoxicity. The IC50 doses were 4.4 and 0.38 .mu.M for the targeted conjugates P(GFLG)-ADR-Ab and P-(G - Mce6-Ab (with light), respectively. Biorecognition was shown to be specific by inhibition experiments with free Ab. The findings indicate the potential of these conjugates as effective agents in the treatment of ovarian cancer.

L27 ANSWER 10 OF 19 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
96328995 EMBASE Document No.: 1996328995. Treatment of ovarian cancer with **photodynamic therapy** and immunoconjugates in a murine ovarian cancer model. Goff B.A.; Blake J.; Bamberg M.P.; Hasan T., Massachusetts General Hospital, Wellman Laboratories Photomedicine, 55 Fruit Street,Boston., MA 02114, United States. British Journal of Cancer 74/8 (1194-1198) 1996.
ISSN: 0007-0920. CODEN: BJCAAI. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB In **photodynamic therapy** (PDT), photosensitisers accumulate somewhat preferentially in malignant tissues, photoactivation with appropriate wavelength of light releases toxic molecular species which lead to tumour tissue death. In order to target ovarian cancer with increased specificity, a **chlorin**-based photosensitiser (**chlorin** e6 monoethylendiamine monoamide) was conjugated to OC125, a monoclonal **antibody** recognising an antigen expressed in 80 of non-mucinous ovarian cancers. In previous work, this immunoconjugate (IC) was shown to be selectively phototoxic to cancer cells from ovarian cancer patients ex vivo and to localise preferentially in ovarian cancer tissue in vivo. In this study we report results from in vivo phototoxicology and photodynamic treatment studies using this IC in a murine model for ovarian cancer. A comparison of single vs multiple treatments was also made. For in vivo experimentation, Balb C nude mice were injected with 30 x 106 NIH:OVCAR 3 cancer cells to create an ascitic tumour model. Animals were then given intraperitoneal injections of the immunoconjugate (0.5 mg kg-1). Twenty-four hours later the intraperitoneal surfaces were exposed to 656 nm light from an argon-ion pumped-dye laser (50 mW, 656 nm), using a cylindrical diffusing tip fibre. The overall treatment was given either once or multiply. No animals died from treatment complications. Twenty-four hours following one and three PDT treatments, the percentage of viable tumour cells in the ascites of the treated animals analysed ex vivo was 34 and 5 of control for one and three treatments respectively. With respect to survival, all control mice (n = 18) died between 30 and 50 days. However, for those treated three times (n = 10), 40 were still alive after 5 days, and for those treated four times (n =) 58 were alive after 5 days. Evaluation with log-rank test revealed a significant survival with intraperitoneal PDT compared with controls (P = 0.0006). These preliminary results suggest that PDT with an OC125 immunoconjugate may be an effective therapy for the management of advanced ovarian cancer. Clinical application of this therapy needs to be further optimised and may require multiple treatments, similar to fractionated radiation therapy and cyclic chemotherapy, in order to control malignant disease with acceptable toxicity to normal tissue.

L27 ANSWER 11 OF 19 SCISEARCH COPYRIGHT 2003 ISI (R)
ANTIBODY

L27 ANSWER 2 OF 19 CAPLUS COPYRIGHT 2003 ACS
2001:597738 Document No. 135:149263 Methods and compositions for treating condition of the eye. Miller, Joan W.; Gragoudas, Evangelos S.; Renno, Reem Z. (Massachusetts Eye and Ear Infirmary, USA). PCT Int. Appl. WO 2001058344 A2 20010816, 44 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US4161 20010209. PRIORITY: US 2000-PV181641 20000210.

AB Provided are methods and compns. for the **photodynamic therapy** (PDT) of ocular conditions characterized by the presence of unwanted choroidal neovasculature, for example, neovascular age-related macular degeneration. The selectivity and sensitivity of the PDT method can be enhanced by combining the PDT with an anti-angiogenesis factor, for example, angiostatin or endostatin, or with an apoptosis-modulating factor. Furthermore, the selectivity and sensitivity of the PDT may be further enhanced by coupling a **targeting** moiety to the photosensitizer so as to target the photosensitizer to choroidal neovasculature.

L27 ANSWER 3 OF 19 CAPLUS COPYRIGHT 2003 ACS
2001:100998 Document No. 134:127882 Dendrimer-photosensitizer complexes for medical applications. Roder, Beate; Hackbarth, Steffen; Wohlecke, Gisela (Biolitec Ag, Germany; Biolitec Inc.). PCT Int. Appl. WO 2001008704 A2 20010206, 11 pp. DESIGNATED STATES: W: BR, CA, CN, JP, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (English). CODEN: PIXXD2. APPLICATION: WO 2000-IB1165 20000728. PRIORITY: DE 1999-19936997 19990803.

AB A method for enhanced **photodynamic therapy** (PDT) treatments by applying dendrimer-photosensitizer complexes to bring multiple photosensitizer moieties to a treatment site is provided. Photosensitizers are covalently coupled to the peripheral bonding places of dendrimers and are being sepd. in one or more successive cycles. Tetrapyrroles are the photosensitizers employed. In one embodiment, the complex is also bound to an **antibody** or **antibody** fragment, which aids in **targeting** the complex to a desired treatment site. After application, the photosensitizers are released, at the treatment site, from the complexes by either light, chem., or a combined light/chem. effect. Generally the photosensitizers develop their full photodynamic activity as free mols. after being released from the complex. More than one type of photosensitizer may be bound in the complexes. Release and/or activation may be done in a single step or with repeated steps.

L27 ANSWER 4 OF 19 BIOSEARCH COPYRIGHT 2003 ISI (R)
2001:[illegible] The Genuine Article (R) Number: 479PB. Pegylation of a **chlorin**(e6) polymer conjugate increases tumor **targeting** of photosensitizer. Hamblin M R; Miller J L; Rizvi I; Ortel B; Maytin E V; Hasan T (Reprint). Massachusetts Gen Hosp, Wellman Labs Photomed, Dept Dermatol, 50 Blossom St WEL224, Boston, MA 02114 USA (Reprint); Massachusetts Gen Hosp, Wellman Labs Photomed, Dept Dermatol, Boston, MA 02114 USA; Harvard Univ, Sch Med, Dept Dermatol, Boston, MA 02115 USA; Harvard Univ, Sch Med, Dept Mol Endocrinol, Boston, MA 02115 USA. CANCER

AB **Photodynamic therapy** is emerging as a viable modality for the treatment of many cancers. A limiting factor in its use against intracavity tumors such as disseminated ovarian cancer is insufficient selectivity of the photosensitizer for tumor compared with normal tissue. We report on an approach to improve tumor **targeting** by exploiting differences between cell types and by chemical modification of a photosensitizer conjugate. Attachment of polyethylene glycol (pegylation) to a polyacetylated conjugate between poly-l-lysine and **chlorin** (c6) increased the relative phototoxicity in vitro toward an ovarian cancer cell line (OVCAR-5) while reducing it toward a macrophage cell line (J774), compared with the nonpegylated conjugate. Surprisingly, the increased phototoxicity of the pegylated conjugate correlated with reduced oxygen consumption. Pegylation also reduced the tendency of the conjugate to aggregate and reduced the consumption of oxygen when the conjugates were illuminated in solution in serum containing medium, suggesting a switch in photochemical mechanism from type II (singlet oxygen) to type I (radicals or electron transfer). Pegylation led to more mitochondrial localization as shown by confocal fluorescence microscopy in OVCAR-5 cells, and, on illumination, produced a switch in cell death mechanism toward apoptosis not seen with J774 cells. Conjugates were injected i.p. into nude mice bearing i.p. OVCAR-5 tumors, and the pegylated conjugate gave higher amounts of photosensitizer in tumor and higher tumor:normal tissue ratios and increased the depth to which the **chlorin** (c6) penetrated into the peritoneal wall. Taken together, these results suggest that pegylation of a polymer-photosensitizer conjugate improves tumor-**targeting** and may increase the efficacy of **photodynamic therapy** for ovarian cancer.

L27 ANSWER 5 OF 19 CAPLUS COPYRIGHT 2003 ACS

2000:493418 Document No. 133:101471 Transcutaneous photodynamic treatment of targeted cells. Chen, James (Light Sciences, Ltd., USA). PCT Int. Appl. WO 2000041727 A1 20000720, 62 pp. DESIGNATED STATES: W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GF, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US944 20000114. PRIORITY: US 1999-PV116284 19990115; US 1999-271575 19990318.

AB The present invention is drawn to methods and compds. for **photodynamic therapy** (PDT) of a target tissue or compns. in a mammalian subject, using a light source that preferably transmits light to a treatment site transcutaneously. The method provides for administering to the subject a therapeutically effective amt. of a targeted substance, which is either a targeted photosensitizing agent, or a photosensitizing agent delivery system, or a targeted prodrug. This targeted substance preferably selectively binds to the target tissue. Light at a wavelength or waveband corresponding to that which is absorbed by the targeted substance is then administered. The light intensity is relatively low, but a high total fluence is employed to ensure the activation of the targeted photosensitizing agent or targeted prodrug product. Transcutaneous PDT is useful in the treatment of specifically selected target tissues, such as vascular endothelial tissue, the abnormal vascular walls of tumors, solid tumors of the head and neck, tumors of the gastrointestinal tract, tumors of the liver, tumors of the breast, tumors

tumor cells is not always sufficient for PDT to be efficient. In recent years targeted PDT (TPDT) has been developed in attempts to improve PS selective location in tumors by means of binding PSs to **targeting** (address) molecules such as **antibodies** (Abs), lectins, hormones, etc. In using TPDT, a new selectivity factor is added: high affinity of the **targeting** molecule for the respective tumor-associated antigen or receptor. This review deals with modern approaches to constructing targeted PSs (TPSs) as well as with the mechanism, prospects and limitations of TPDT application in the treatment of tumors.

L27 ANSWER 14 OF 19 MEDLINE
93188049 Document Number: 93188049. PubMed ID: 8445672.
Photodynamic therapy in oncology: mechanisms and clinical use. Pass H I. (Thoracic Oncology Section, NCI/NIH, Bethesda, MD 20892.) JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1993 Mar 17) 85 (6) 443-56. Ref: 214. Journal code: 7503089. ISSN: 0027-8874. Pub. country: United States. Language: English.

AB In **photodynamic therapy** (PDT), a sensitizer, light, and oxygen are used to cause photochemically induced cell death. The mechanism of cytotoxicity involves generation of singlet oxygen and other free radicals when the light-excited sensitizer loses or accepts an electron. Although selective retention of sensitizer by malignant tissue is seen in vivo, the mechanisms for this sensitizer **targeting** remain unclear. The first-generation sensitizers are porphyrin based and vary in lipophilicity and hydrophilicity. **Targeting** of the vasculature seems to be a prominent feature of the cytotoxic effect of these sensitizers in vivo, with resulting necrosis. Treatment depth varies with the wavelength of light that activates the sensitizer used, and the second-generation sensitizers are activated at longer wavelengths, allowing for a 30% increase in treatment depths. The selectivity of **targeting** can be increased when the sensitizer is delivered with the use of liposomes or monoclonal **antibodies** specific for tumor antigens. Studies have demonstrated direct effects of PDT on immune effector cells, specifically those with lineage from macrophages or other monocytes. Clinically, this therapy has been chiefly used for palliation of endobronchial and esophageal obstruction, as well as for treatment of bladder carcinomas, skin malignancies, and brain tumors. The future of PDT rests in defining its use either as an intraoperative adjuvant to marginal surgical procedures or as a primary treatment for superficial malignancies. Phase III trials in esophageal cancer and lung cancer are in progress and will help in evaluation of whether Photofrin II, the most widely used sensitizer, can be added to the oncologic armamentarium, pending approval from the U.S. Food and Drug Administration.

L27 ANSWER 15 OF 19 SCISEARCH COPYRIGHT 2003 ISI (R) DUPLICATE 3
93:134179 The Genuine Article (R) Number: KP539. PHOTOPROPERTIES OF A MESOCHLORIN E6-N-(2-HYDROXYPROPYL)METHACRYLAMIDE COPOLYMER CONJUGATE. SPIKES J D (Reprint); KRINICK N L; KOPECEK J. UNIV UTAH, DEPT BIOL, SALT LAKE CITY, UT, 84112 (Reprint); UNIV UTAH, DEPT BIOENGN, SALT LAKE CITY, UT, 84112; UNIV UTAH, DEPT PHARMACEUT, SALT LAKE CITY, UT, 84112. JOURNAL OF PHOTOCHEMISTRY AND PHOTOBIOLOGY A-CHEMISTRY (15 FEB 1993) Vol. 70, No. 2, pp. 163-170. ISSN: 1010-6030. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB In the **photodynamic therapy** (PDT) of tumors, improved efficiency of photosensitizer delivery to tumor cells and tumors can sometimes be obtained by binding them to monoclonal **antibodies** or other proteins, particulate materials, and certain types of synthetic water soluble polymers. Synthetic polymers are of particular interest as

targeting

alters their spectral and photosensitizing properties. This paper describes the effects of covalently binding the photosensitizer, mesochlorin e6 monoethylenediamine (CM), to a model N-(2-hydroxypropyl)methacrylamide (HPMA) copolymer on its spectral, photophysical, photosensitizing and photobleaching properties in aqueous solution. Binding had little effect on the spectrum or triplet lifetime of CM, but significantly decreased the bimolecular quenching constant of oxygen for the **chlorin** triplet. Binding also reduced the quantum yield of singlet oxygen production by illuminated CM from 0.73 to 0.25. Photo-oxidation efficiencies for furfuryl alcohol and certain biomolecules were also decreased. Addition of a cationic detergent to the CM-HPMA copolymer increased the yield of singlet oxygen production and the photosensitizing efficiency up to the levels of the free sensitizer. Binding CM to the HPMA copolymer significantly increased its resistance to photobleaching.

L27 ANSWER 16 OF 19 SCISEARCH COPYRIGHT 2003 ISI (R) DUPLICATE 4
93:385146 The Genuine Article (R) Number: LG874. TARGETABLE PHOTOACTIVATABLE DRUGS .3. INVITRO EFFICACY OF POLYMER-BOUND **CHLORIN**-E6 TOWARD HUMAN HEPATOCARCINOMA CELL-LINE (PLC/PRF/5) TARGETED WITH GALACTOSAMINE AND TO MOUSE SPLENOCYTES TARGETED WITH ANTI-THY 1.2 **ANTIBODIES**.
PINOVA S (Reprint); KRINICK N L; KOPECEK J. CZECHOSLOVAK ACAD SCI, INST MICROBIOL, CS-14220 PRAGUE 4, CZECHOSLOVAKIA (Reprint); UNIV UTAH, DEPT BIOENGN, SALT LAKE CITY, UT, 84112; UNIV UTAH, DEPT PHARMACEUT & PHARMACEUT CHEM, SALT LAKE CITY, UT, 84112. JOURNAL OF CONTROLLED RELEASE (27 MAY 1993) Vol. 25, No. 1-2, pp. 71-87. ISSN: 0168-3659. Pub. country: CZECHOSLOVAKIA; USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Chlorin** e6 and HPMA copolymer-bound **chlorin** e6 were compared with **chlorin** e6 polymer conjugates containing galactosamine or anti-Thy 1.2 **antibody** as **targeting** moieties. Galactosamine recognizes asialoglycoprotein receptors on the human hepatocarcinoma cell line PLC/PRF/5 and the anti-Thy 1.2 **antibody** interacts with Thy 1.2 alloantigens on mouse splenic T cells. The efficiency of photodynamic injury as a function of incubation time and temperature, and irradiation time was studied.

Two-day-old cultures of PLC/PRF/5 cell line were most sensitive to HPMA copolymer bound **chlorin** e6 (targeted or nontargeted), whereas no differences were observed when free drug was tested on 1-, 2-or 3-day-old cultures. Dark toxicity of the free drug was observed at concentrations as low as 2 X 10(-6) M. Dark toxicity decreased when **chlorin** e6 was bound to HPMA copolymers, especially to conjugates containing **targeting** moieties.

The effect of incubation time was seen only in the hepatocarcinoma cell culture. For galactosamine-targeted HPMA copolymer bound **chlorin** e6, 2-3 h were necessary to induce a pronounced killing effect. For anti-Thy 1.2 targeted polymeric drug and for free **chlorin** e6, 1 h of incubation was sufficient to load the cells with a photolytic dose of **chlorin** e6. Dependence on the time of irradiation was observed in both targeted conjugates. One hour of irradiation induced only limited photolysis, whereas 7.5 h of irradiation was necessary for substantial photodynamic injury. Photodynamic destruction of cells exposed to free drug was similar for irradiation periods of 1-7.5 h. In accordance with the mechanism of cellular uptake of polymeric conjugates by receptor mediated endocytosis, the conjugates were less photodynamically active when incubated with cell cultures at a lower (4-degrees-C) temperature. Nontargeted polymeric **chlorin** e6 was always considerably less phototoxic when compared to targeted HPMA copolymer

concentrations of the photosensitizer do not destroy (desintegrate) the target cells, but their function and/or proliferation may be impaired.

Binding of **antibodies** via carbohydrate moieties in the Fc portion of the anti-Thy 1.2 molecule increases the photodestructive capacity of the **antibody** targeted photosensitizer, when compared to conjugates where the **antibody** was bound via N(epsilon)-amino groups of lysine residues. A concentration of 1 X 10(-7) M of **chlorin** e6 in the former conjugate kills 4[illegible], and a concentration of 1 X 10(-6) M 80% of target T cells while the latter conjugate and free drug are ineffective at the above mentioned concentrations.

The results obtained from these two in vitro models allowed us to compare the photodynamic effect of targeted HPMA copolymer bound **chlorin** e6 on a hepatocarcinoma cell line (model of anticancer treatment) and on normal lymphocytes (model of immunosuppression).

L27 ANSWER 17 OF 19 CAPLUS COPYRIGHT 2006 ACS
1992:190281 Document No. 116:190281 Targetable photoactivatable drugs. Rihova, B.; Kopecek, J. (Inst. Microbiol., Czech. Acad. Sci., Prague, CS-142 20, Czech.). Journal of Materials Science: Materials in Medicine, 2 4), 238-42 (English) 1991. CODEN: JSMMEL. ISSN: 0957-4530.

AB The photodynamic activity of photosensitizer **chlorin** e6 and its targeted or nontargeted polymeric derivs. were evaluated on the human hepatocarcinoma cell line PLC PRF 5 (**targeting** structure was galactosamine) or on mouse T splenocytes (**targeting** structures were anti Thy 1.2 **antibodies**). It was found that the targeted conjugate is up to 500 hundred times more phototoxic than its nontargeted counterpart. Photodynamic activity of polymeric **chlorin** e6 targeted with ATS-A (randomly bound **antibody**) was detected up to the concn. of 1 .times. 10-6M (0.65 .mu.g drug/mL), while photodynamic activity of polymeric **chlorin** e6 targeted with ATS-C (oriented binding of **antibody** via their Fc part) was detected up to the concn. of 1 .times. 10-8M (0.0065 .mu.g drug/mL). The final photodynamic effect was dependent on the time and temp. of incubation and on the time of irradn.

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91:417616 The Genuine Article (R) Number: FX482. TARGETABLE PHOTOACTIVATABLE POLYMERIC DRUGS. KOPECEK J (Reprint); RIHOVA B; KRINICK N L. UNIV UTAH, CCCI, 421 WAKARA WAY, SUITE 318, SALT LAKE CITY, UT, 84108 (Reprint). JOURNAL OF CONTROLLED RELEASE (1991) Vol. 16, No. 1-2, pp. 137-143. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The design of targetable polymeric photoactivatable drugs based on N-(2-hydroxypropyl)methacrylamide (HPMA) copolymers is described. Two types of conjugates have been synthesized: (a) HPMA copolymer-galactosamine-**chlorin** e6 conjugates; and (b) HPMA copolymer-anti-Thy 1.2 **antibody**-**chlorin** e6 conjugates. Their photodynamic activity was evaluated in vitro. The conjugate containing galactosamine as the **targeting** moiety was tested on a human hepatoma cell line PLC PRF 5; Alexander cells, containing the asialoglycoprotein receptor. It was shown that the targetable conjugate was more active in vitro when compared with an HPMA copolymer-**chlorin** e6 conjugate. The photodynamic activity of two HPMA copolymer-anti-Thy 1.2 **antibody**-**chlorin** e6 conjugates was evaluated towards mouse splenocytes in vitro. They differ in the method of **antibody** binding. One contained anti-Thy 1.2 **antibodies** bound via N-epsilon-amino groups of lysine residues, [illegible] **antibodies** [illegible]

antibodies bound via carbohydrate groups was the most active both in its photodynamic effect on the viability of splenocytes and the suppression of the primary **antibody** response of mouse splenocytes towards sheep red blood cells in vitro.

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1987:276093 Document No.: BA84:17132. **PHOTODYNAMIC THERAPY** OF TUMORS AND OTHER DISEASES USING PORPHYRINS. SPIKES J D; JORI G. DIP. DI BIOL., UNIV. DEGLI STUDI DI PADOVA, VIA LOREDAN 10, 35131 PADOVA, ITALY.. LASERS MED SCI, (1987) 2 (1-, 4-19. CODEN: LMSCEZ. Language: English.

AB **Photodynamic therapy** (PDT) with porphyrins and red light (620-650 nm) is finding increasing clinical application for both the eradication of relatively small tumours and the palliation of inoperable or obstructive tumours. PDT also shows some promise for the sterilization of the tumour bed after surgical removal of neoplasmic masses. Several porphyrins have been found to be accumulated and retained by tumour tissues; however, a chemically prepared derivative of haematoporphyrin, termed HpD, and a purified form of HpD, termed DHE (dihaematoporphyrin ether or ester), are most frequently used in clinical practice owing to their optimal tumour-localizing properties and low systemic toxicity in the dark. The efficiency of HpD/DHE photoactivation by red light is very low, since their extinction coefficient at wavelengths above 600 nm is below 10$3 M-1 cm-1. Therefore, a large number of investigations are being performed in order to improve the efficacy of PDT. One approach involves the use of porphyrin analogs (e.g., **chlorins**, phthalocyanines) which retain a high affinity for tumours and possess intense absorption bands in the red spectral region. Moreover, the selectivity of tumour **targeting** can be enhanced by transport of the photosensitizing drug with some types of lipoproteins or monoclonal **antibodies**. These developments are of interest also in view of the proposed extension of PDT to the treatment of other diseases, including viral and microbial infections, atheroma and psoriasis.

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